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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

SUMITOMO DAINIPPON PHARMA CO., LTD. and SUNOVION PHARMACEUTICALS INC., Plaintiffs, v. EMCURE PHARMACEUTICALS LIMITED, *et al.*, Defendants.	Civil Action No. 15-280 (SRC) (CLW) Civil Action No. 15-281 (SRC) (CLW) Civil Action No. 15-6401 (SRC) (CLW) (Consolidated)

DECLARATION OF PRESTON K. RATLIFF II IN SUPPORT OF SUNOVION'S RESPONDING CLAIM CONSTRUCTION BRIEF

I, Preston K. Ratliff II, am a Partner at the law firm of Paul Hastings LLP, 200 Park Avenue, New York, New York 10166, counsel for Plaintiffs Sumitomo Dainippon Pharma Co., Ltd. and Sunovion Pharmaceuticals Inc. (collectively, "Sunovion") in this matter. I make this declaration in support of Sunovion's Responding Claim Construction Brief.

1. Attached as Exhibit 10 is a true and correct copy of excerpts from the transcript of the July 14, 2016 deposition of Dr. Steven W. Baldwin.
2. Attached as Exhibit 11 is a true and correct copy of excerpts from the transcript of the July 21, 2016 deposition of Dr. Stephen G. Davies.
3. Attached as Exhibit 12 is a true and correct copy of U.S. Patent No. 4,681,893, as provided to Dr. Steven W. Baldwin in his July 14, 2016 deposition.

I declare under penalty of perjury that the foregoing is true and correct.

Dated 8/16/16

Preston K. Ratliff II

EXHIBIT 10

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY
----------X
SUMITOMO DAINIPPON PHARMA CO., LTD.
and SUNOVION PHARMACEUTICALS, INC.,
Plaintiffs,

v.

EMCURE PHARMACEUTICALS USA, INC.
and EMCURE PHARMACEUTICALS LTD.,
Defendants.
----------X

July 14, 2016
9:02 a.m.

Videotaped Deposition of STEVEN WORTH BALDWIN, pursuant to notice, at the offices of Blank Rome LLP, 405 Lexington Avenue, New York, New York, before Mark Richman, a Certified Shorthand Reporter, Registered Professional Reporter and Notary Public within and for the State of New York.

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Michael Drenkalo, Videographer

E X H I B I T S

(Whereupon Baldwin Exhibit 10 was marked for identification, document depicting a structure.) 180 24

(Whereupon Baldwin Exhibit 11 was marked for identification, copy of U.S. Patent 4,681,893.) 183 3

(Whereupon Baldwin Exhibit 12 was marked for identification, copy of the declaration of Dr. Steven G. Davies.) 241 7

(Whereupon Baldwin Exhibit 13 was marked for identification, Opening brief in support of the plaintiff's claim construction in this litigation.) 250 3

STEVEN WORTH BALDWIN

THE VIDEOGRAPHER: Now recording and on the record. My name is Michael Drenkalo, certified legal video specialist for DTI. Today's date is July 14, 2016, time is 9:02 a.m.

We are at the offices of Blank Rome LLP, 405 Lexington Avenue, New York, New York to take the video deposition of Professor Steven Baldwin in the matter of Sumitomo Dainippon Pharma Co. Ltd. And Sunovion Pharmaceuticals Inc. versus Emcure Pharmaceuticals USA, Inc. and Emcure Pharmaceuticals Ltd., United States District Court District of New Jersey.

If counsel will please introduce themselves for the record.

MR. RATLIFF: Preston Ratliff, with the Paul Hastings law firm in New York, on behalf of the plaintiffs, and here with me today are Leo DeSesso and Mike McCrane, also with the Paul Hastings law firm. And also here with me today is Michelle Flores from

STEVEN WORTH BALDWIN

Sunovion.

MR. HU: Chris Hu and David Kistler, from Blank Rome, for Emcure.

MR. PREW: Brian Prew from Goodwin Procter on behalf of Teva.

MR. GUERRIERO: Salvatore Guerriero of Caesar Rivise on behalf of defendant InvaGen Pharmaceuticals Inc.

THE VIDEOGRAPHER: Our court reporter today is Mark Richman of DTI who will now swear in the witness.

STEVEN WORTH BALDWIN, Having been called as a witness, having been first duly sworn by the Notary Public (Mark Richman), was examined and testified as follows:

EXAMINATION BY MR. RATLIFF:

Q. Good morning, sir.

A. Good morning.

Q. Please state your full name for the record.

A. Steven Worth Baldwin.

Q. Please state your residence

STEVEN WORTH BALDWIN

address for the record.

A. 5209 Piney Hollow Court, Durham, North Carolina.

Q. How are you feeling today?

A. Fine.

Q. Is there any reason you cannot give truthful and accurate testimony today?

A. No, there's no reason.

Q. And you've had your deposition taken before, correct?

A. Yes, I have.

Q. You've had it taken many times before, correct?

A. Yeah, many is a relative word, but something over between 20 and 30 would be my best guess over a 20-year period.

Q. You consider that many, correct?

A. Yeah, that's fine.

Q. Now, one of your professional activities is being a scientific consultant for several major intellectual

A. Yea. I believe that's right but I'm not...

MR. RATLIFF: So let's do this. I'd like the court reporter to mark this as Baldwin Exhibit Number 2.

(Whereupon Baldwin Exhibit 2 was marked for identification, handwritten drawing of the witness.)

Q. And, professor, I'll hand this back to you. I just want to make some clarifications on it. Professor Baldwin, if you could just put a 1 to the left of the structure.

A. And --

Q. Just put a 1.

A. One, Roman?

Q. Numeral.

A. Arabic?

Q. Whatever you prefer. Great. Okay. Now --

MR. HU: Excuse me, is that a label that you're just identifying

this as 1 on some kind of list?

MR. RATLIFF: We'll we're not in the list yet.

MR. HU: Well I'd like to know just what the 1 is for, that's all, for clarification here?

MR. RATLIFF: Well, listen --

MR. HU: I mean you're having him write things. Can you tell us what it is?

MR. RATLIFF: Listen. Listen, and you'll get it.

Q. So, Professor Baldwin, are there various substructures that are found in lurasidone?

A. I'm not quite sure what you mean.

Q. Have you ever used the term molecular substructure?

A. I mean it's a term that is used to talk about a particular region within a larger molecule. But I mean I could describe, you know, probably 15 substructures. So I'm not quite sure at

what level you're, you're, you know, you're discussing.

Q. Okay. So that, so that we're clear, could you describe lurasidone in 15 substructures?

A. Well, you know, I'm not, I'm not sure. I mean there isn't a precise number of substructures to this. It depends on how, you know, how much you want to drill down.

Q. Okay. So there's no set definition as to how many substructures are in the molecule lurasidone?

A. That's right. As I look at this, I clearly see either three or four areas in the molecule that one could talk about as being substructures conveniently, but there's others. There's additional ones. Each of those substructures has substructures associated with it.

Q. Fair enough. Fair enough. And to the right of the structure, can you just write the word lurasidone so

that we understand what it is?

A. Well, again, you know, I do have a question here. I'm not a hundred percent sure. And so what I don't want to the do is write lurasidone and then have you come back and, you know, attack me for having exactly the wrong stereochemistry at that point.

Q. No one is trying to attack you. If you want, you can write attempt at drawing or depicting lurasidone if you want. I'm just trying to separate that from what we do next. Great.

And is there a reason that you're having difficulty recalling the stereochemistry with respect to the cyclohexyl lurasidone?

A. Well, I mean what I know is that relative to this six membered ring here, one group is up, one group is down so they're trans. I know. And I probably should have checked this and I just can't remember right now if it was -- if it's this way, that is the left

racemic mixture?

A. Well, I mean again there's several ways that one could do that.

Q. Okay.

A. But typically what one would do would be to pick one of these two structures and draw that structure.

Q. Okay.

A. Okay. And then if there was no indication that that structure was a single enantiomer, the assumption would be that it represented a racemic mixture of the two compounds.

Q. Okay. But you can, you can pick either one to represent a racemic mixture, correct?

A. Yes, that's correct.

Q. Okay. And is it your view that if a single structure is depicted, it always represents a racemic mixture?

A. I mean that's -- I mean that's -- by -- I'm going to use the word convention. I'm not, I'm not suggesting that that's adopted by, you know, a

scientific body. But the convention is that the structure, standalone structure is meant to represent a racemic version of that material, unless there's an indication that is, you know, you could imagine several indications, like plus or minus small d small l, given the configurations of the carbons in question right there. That would mean that it was a single enantiomer.

And it's, the issue is that it's just, it's a convenience issue to save one the time of drawing two structures.

Q. In your response you mention the words standalone structure. What do you mean by standalone structure?

A. Yes, could I hear, may I hear what I said?

(The requested portion of the record was read.)

A. Okay. Now, by standalone structure what I meant was that the structure with no additional information

provided that would suggest that it was a single enantiomer. Then the assumption is that it's not a single enantiomer and that is in fact it's a racemic mixture with only one of the enantiomers being shown.

Q. When you -- when you read the '372 patent, did you come across any standalone structure?

A. Of anything?

Q. Of anything.

A. Well there's, yes, there's structures, you know, throughout the patent that are, that are, that are standalone structures.

Q. Okay. So I guess I'm trying to understand a little bit more about what you mean by a standalone structure. Would the information that's contained in the patent specification of the '372, would that be -- would you exclude that from being information that relates to the structure?

A. No. Again, I think I, I think

I understand the question.

Q. Okay.

MR. HU: Well if you don't, Professor Baldwin, just say so.

MR. RATLIFF: He's an expert. He's done this many times.

MR. HU: Well, I know.

MR. RATLIFF: He knows --

MR. HU: He said he doesn't understand.

MR. RATLIFF: You don't have to coach the witness.

MR. HU: I'm not coaching him. I'm just suggesting if he expresses concern.

MR. RATLIFF: Suggesting is coaching. Come on now.

MR. HU: Ask a better question.

A. Now I've lost my train of thought so can we try that again?

Q. Okay.

MR. RATLIFF: You really shouldn't interrupt. That just

wastes your witness's time.

MR. HU: That's an objection.

MR. RATLIFF: You really shouldn't do that.

MR. HU: We've been very patient, come on.

Q. Okay. So and let's try to set aside what, your counsel's, your counsel's interruptions and let's just focus because we were in a good place.

I'm trying to understand what you mean by standalone structure. Let's take, for example, Claim 14 of the '372 patent. Does that contain in your view a standalone structure?

A. Yes, it does.

Q. Now, are there words that are in the claim that's associated with the structure?

A. There are. I would, you know, I'd like -- can I open, may I open up?

Q. Absolutely.

A. Yes, there are words.

Q. Even though there are words in

Claim 14 in addition to the structure, you still would consider Claim 14 to contain a standalone structure?

A. Well, by standalone I mean a structure that has no additional stereochemical designation associated with it. And so there's no -- these words don't contain any stereochemical information.

And so this is a standalone structure from the stereochemical point of view which is what we're talking about here.

Q. Did you examine the '372 patent specification to determine whether or not there was additional stereochemical designation associated with the structure in Claim 14?

A. Yes, I did.

Q. And what was the result of your examination?

A. Well, virtually the same structure shows up earlier, although the earlier structure specifically shows it

as a hydrochloride salt. But just looking at the organic part of this, virtually the same structure shows up at the bottom of column 30 in the patent.

Q. Okay. Not the same structure, a different structure shows up?

A. Well, just a minute. I mean it's the same structure except for the HCL and of course the Compound 101 designation below it right there. In other words, this structure, the organic part of the compound at the bottom of column 30, which is indicated as 101, is probably superimposable on this one right here. I mean I haven't tried to do it. But every stereochemical center is the same, is identical.

Q. My question is a little bit different.

A. Okay.

Q. My question is whether or not the structure that you found in the patent specification was the same as the structure in Claim 14. So are they the

same or are they different?

A. Well, again, they're different in that there's an HCL salt here. There's not an HCL salt over in the claim.

Q. Thank you.

A. But the organic chemistry part is the same.

Q. And I don't know what's meant by the organic chemistry part. But my question is not about the organic chemistry, it's about the entire structure and I think I have -- well I know I have the answer, thanks.

A. Well, may I ask by your question were you asking about the salt, the acid addition salt portion of it?

Q. I can try it again. And I think it's pretty clear, straight forward. Is the structure that you found in the '372 patent, the entire structure, identical to the structure that's in Claim 14, yes or no?

MR. HU: Objection, he

answered. That's been asked and answered twice.

A. It's not a yes or no question. This specifically shows an HCL molecule with the free base part. The structure in Claim 14 doesn't, although it mentions acid addition salts. So I don't know whether that's the -- you know, the business end of this molecule, that is the organic carbon containing part of the molecule right there is identical to the carbon containing part of the molecule in Claim 14.

Q. So you don't know if the structures that are depicted in Claim 14 and in the specification are the same or different?

MR. HU: Objection.

A. Doesn't --

MR. HU: It's asked and answered. You've asked him that three times, he's answered it three times and you're mischaracterizing his testimony now.

MR. RATLIFF: Can you stop interrupting.

MR. HU: I can object. Calm down.

MR. RATLIFF: That's not an objection. You are interrupting. It's not.

A. They're the same structure.

Q. They're the same?

A. They're the same structure.

Q. Okay. So let's -- you have your copy of the Baldwin Exhibit Number 3 which is the '372 patent. Will you please circle the structure that you believe is identical to the structure in Claim 14. Let me see that. Okay.

I noticed when you circled the structure you did not include the HCL that's a part of the structure on the page that includes column 29 and 30; is that correct?

A. The HCL is not circled, yes, that's correct.

Q. Okay. Do you not consider the

HCL to be part of the structure for Compound Number 101?

A. The HCL is part of the structure of, of Compound 101, yes.

Q. Okay.

A. But the, the carbon containing part of molecule 101 that I've circled is the same as the, as the compound that shows up in Claim 14.

Q. Okay. Is there any compound, by number, that's identical to the structure in Claim 14?

A. So is there any numbered compound in here that is identical to claim --

Q. Let me try it this the way. So with respect to Compound Number 101, when you circled it, you excluded the HCL. But you understand that Compound Number 101, in your view, includes the HCL, correct?

A. Yes.

Q. Okay.

A. That's right.

Q. So that compound, its structure as depicted on the columns bridging 29 and 30, is that identical to the structure that's depicted in Claim 14 of the '372 patent?

A. Well, again I think, I think I've been through this. The circled part --

Q. I'm not referring to -- let me be very clear. I'm not referring to the circled part because the circled part is not in your view the entirety of Compound 101. Okay, so that's established. I'm not talking about the circled part.

MR. HU: Objection, ask him a question. Let's not have an argument. Ask him a question.

Q. I'm focusing, I'm focusing, in particular, on the entire structure that includes the HCL as you understand it. Okay?

A. Mm-hmm. Yes.

Q. Is that entire structure identical to the structure that you see

in compound -- strike that.

Is that entire structure identical to the structure you see in Claim 14 of the '372 patent?

A. No, it is not identical.

Q. Okay.

A. The structure shown, specifically shown in Claim 14 is the free base of the -- of Compound 101 in column 30.

Q. All right.

MR. RATLIFF: We've been going for about an hour, let's take a break.

THE VIDEOGRAPHER: Standby. Time is now 10:01 a.m., off the record.

(A recess was had.)

THE VIDEOGRAPHER: Time is now 10:15 a.m., back on the record.

Q. Great, welcome back. Professor, during the break did you discuss this case at all?

A. No.

Q. Did you discuss any of my questions?

A. No.

Q. When you're consulting for litigation, do you make it a point to conduct a careful analysis?

A. That's, I mean that's -- I mean that's, that's a difficult, you know, it's a difficult question. I mean I'm very careful with what I'm asked to do and to do a thorough job with the job that I'm tasked with. But I -- that's enough, yes.

Q. Okay. For this particular case did you act with care in providing your opinions and analysis?

A. Yes, within the, again, with what I was asked to do.

Q. Okay. What were you asked to do?

A. Okay. I was asked to give my opinion about Claim 14 and the '372 patent and, you know, any other documents that, that would have been, would be

provided to me.

Q. Specifically, what opinion were you asked to give with respect to Claim 14 of the '372 patent?

A. Well, the, you know, we had an initial conversation and the question was what in my view, what did Claim 14 mean? And, you know, it was -- and I can't remember if specifically they asked but, you know, is it, one, an enantiomer, is it a racemic mixture. In other words, relating to the, the questions were relating to the stereochemistry as depicted in that structure.

Q. Did they give you choices as to what Claim 14 could possibly mean?

A. Not, again I'm not quite sure. Again, looking at the structure, there's, there's, you know, a limited number of possibilities. It's either a racemic mixture or a single, you know, realistically, or a single enantiomer.

Q. In your view there's no other possibilities as to what Claim 14 could

mean?

A. I mean -- okay. So people, you know, it's certainly possible to have something other than a hundred/zero situation or a 50/50 situation. I mean that is a possibility. But that's not something that you typically can, would ferret out or expect to be able to interpret, you know, just based on those structures without looking at any, you know, any textual material.

Q. And what do you mean by not being a zero to --

A. Hundred.

Q. -- hundred situation or a 50 to 50 situation?

A. Well, I mean the normal -- you know, the two real extremes are that it is one and only one enantiomer or that it is a 50/50 mixture, that is an enantiomeric of a racemic mixture, you know, of the compounds. And those are the normal extremes that people would encounter.

again. Did you see within the file history of the '372 patent any indication that the applicants had identified lurasidone hydrochloride, or Compound 105, as being covered by Claim 14?

A. Right now I don't remember, to tell you the truth. I just don't recall.

Q. Okay. And if you, and if you did, do you think if you did see something that gave an indication, you would have spoken about that in your declaration?

A. It, you know, it depends on, it would depend on what it said and what the context was.

Q. Are you finished?

A. Yes.

Q. Okay.

MR. RATLIFF: I'd like the court reporter to mark a multipage document as Baldwin Exhibit Number 5.

(Whereupon Baldwin Exhibit 5 was marked for identification,

Bates stamp LATUDA-00000849 through 852.)

Q. Dr. Baldwin, do you recognize Baldwin Exhibit Number 5?

A. This is, yes, this was part of the file history.

Q. Okay. So this was, this was one of the documents that you reviewed prior to submitting your declaration concerning claim construction, correct?

A. I'm not -- I certainly scrolled through it. I'm not sure that I, that I read it carefully beforehand. This thing is dated much later than the, when the, the PTO was reviewing this thing.

Q. Okay. And -- sorry. My question wasn't about you reading it carefully.

A. Right. Well I saw this then. For sure.

Q. That's all.

A. Yes.

Q. You saw this document?

A. Yes.

Q. Prior to submitting your declaration?

A. I certainly did see this document, yes, before I submitted the declaration.

Q. Thank you.

MR. RATLIFF: I'd like the court reporter to mark a multipage document as Baldwin Exhibit Number 6.

(Whereupon Baldwin Exhibit 6 was marked for identification, Bates stamp LATUDA-00000970 through 972.)

Q. Professor, do you recognize Baldwin Exhibit Number 6?

A. Yes, I've seen this.

Q. Okay.

A. As it is again contained within the file history.

Q. Okay. So you saw this prior to submitting your declaration concerning claim construction of Claim 14?

A. Yes. Again, I saw this, yes.

Q. Now if you could turn back to Baldwin Exhibit Number 5. Do you recall when you saw it, if you understood its contents?

A. I mean when I, when I looked at it it seemed to me to be was just an extension past the normal patent expiration date because of, and I'm not sure it says it here, but I, I think I -- I can't remember. But in any event, because it had taken so long for this thing to have FDA approval.

Q. Okay.

A. Hard to get FDA approval.

Q. Okay.

A. So that was my understanding.

Q. Okay. And if you could turn to page 3 of Baldwin Exhibit Number 5.

A. Okay.

Q. Turning your attention to paragraph 9, where it reads "The patent claims the active ingredient in the approved product LATUDA® (lurasidone

hydrochloride) in at least claims 1, 2, 5, 6, 8(6), 9(6), 10, 11, 12, 13, and 14." Do you see that, sir?

A. I see that, yes.

Q. And turning your attention to where it goes on to say "In particular, Claim 14 reads on the approved product as follows:" Do you see that that?

A. Yes.

Q. Now as you read paragraph 9, do you understand it to be at least the applicant's view that Claim 14 covers the active ingredient lurasidone hydrochloride?

MR. HU: Objection to the form of the question.

A. Yes, the applicant's view as of -- and what is the date of this, the date of the document? It looks like December 2010. So as of 2010, that's what it appears to be, yes.

Q. And do you know whether or not the applicant's had a different view prior to 2010?

A. You know, I don't know.

Q. That's all I was asking, if you know.

A. Yes, right.

Q. And if you could turn your attention to Baldwin Exhibit Number 6, please.

A. Okay.

Q. When you saw this document, that's a copy of a communication from the U.S. Patent Office, did you understand its contents?

A. I mean as I looked at this, it was a response to the application for the extension and the granting of a five-year extension, yes.

Q. Okay.

A. And I understood that then.

Q. Okay.

A. Okay.

Q. And did you understand then that when the U.S. Patent Office granted the request for an extension, the U.S. Patent Office said "A determination has been made that U.S. Patent Number 5,532,372, which claims the human drug product LATUDA® (lurasidone hydrochloride), is eligible for patent term extension under 35 USC Section 156"?

A. I see that, yes.

Q. And did you see that when you first read the document prior to submitting your declaration?

A. Yes, I had seen this, yes.

Q. And did you understand what that had meant when you first read this document?

A. Well I mean at, at the first level it means that five years is added to the, you know, to the patent extension. I, other than that, I'm not sure what you mean.

Q. Okay. Did you know whether or not if the patent office had actually made a determination that the claims of the '372 patent, as set out by the applicants in Baldwin Exhibit Number 5, covered lurasidone hydrochloride?

A. That the claims. I mean, I mean I, I don't think, I don't dispute that at least some of the claims cover lurasidone hydrochloride. I mean so I'm not quite sure where, where we are.

Q. Right. So where we are is this. In Baldwin Exhibit Number 5 you understood prior to submitting your declaration that the applicants, at least in their view, said that Claim 14 covered lurasidone hydrochloride, and so my question to you is when you saw Baldwin Exhibit Number 6, did you understand that the patent office had made a determination as to whether or not the claims, as set out by the applicants, covered lurasidone hydrochloride?

MR. HU: I'll object to the form of the nonquestion that was the first part of that statement.

Q. Did you understand, sir?

A. I mean what I -- I don't have any idea whether or not, for instance, this first paragraph in exhibit 6 means

that they have gone through and evaluated the claims at that level.

Q. Okay.

A. At this point.

Q. Okay. And when you first read it prior to submitting your declaration, did you think to ask counsel whether or not the U.S. Patent Office had actually made a determination as to whether or not the claims, as identified by the applicants, covered lurasidone hydrochloride?

A. So that the --

Q. Did you think to ask counsel? If you didn't know, if you don't know now, my question to you is at the time that you first read it and prior to submitting your declaration to the court, did you think to ask counsel whether or not the U.S. Patent Office had in fact made such a determination?

A. I mean I know I did not ask, okay.

Q. Now turning to Baldwin Exhibit

Number 4 which is your declaration. Looking again at page 3, paragraph 6.

A. Okay.

Q. In paragraph 6 you identify documents in which your declaration is based, correct?

A. In paragraph 6? Well, yes, the patent file history and then the references that I cite.

Q. Correct. Now the patent is intrinsic evidence, correct?

A. Intrinsic evidence, yes.

Q. The '372 patent file history is intrinsic evidence, correct?

A. That's correct.

Q. But you don't cite any specific portion of the '372 patent file history, correct?

A. I do not, no.

Q. Okay. And the references you cite herein, let's take a look at them. The first one I understand is your CV, correct?

A. Correct.

Q. And that doesn't bear upon the construction of Claim 14, correct?

A. It certainly doesn't.

Q. And the second exhibit is the 372 patent, correct?

A. Yes, it is.

Q. And that's intrinsic evidence as we've already established?

A. Yes.

Q. And then the next several references, exhibits 3 through 14, those are all extrinsic sources, correct?

A. That's correct.

Q. And where did exhibits 3 to 14, where do they come from?

A. You mean -- I mean I'm trying to figure out what you mean. Clearly they come from journal articles.

Q. Okay.

A. Okay.

Q. How did you find them?

A. In fact --

Q. If you did in fact find them? I guess I'm assuming that. Let me try

this again. I'll try to make it easy for you.

Were any of the references of exhibits 3 through 14 presented to you?

A. Yes. So the, the way that this operated is that we were talking about enantiomers of drugs and how their biological activities can be different. I identified several examples, these being among those examples. And but I did not provide references. Counsel then went and found references for the compounds that I had identified.

Q. Okay. So there are a couple of pronouns in there and I just want to make sure I understand what the pronouns mean. We, who is the we?

A. So we is myself and attorneys to whom I was -- Blank Rome attorneys to whom I was --

MR. HU: Let me stop you there, Professor Baldwin. I'm giving you a lot of slack on the process and I'll let it continue a

A. Which? Again, which, which case are you, are you -- I mean I --

Q. Do you know, do you know if you provided --

A. I mean I have worked, yes, in -- on cases that were, you know, part of a New Jersey District Court. I'm not aware of all the district, different districts in, you know, in New Jersey, so.

Q. Okay. I'm just asking. I think I have the answer. That's okay. You would agree that in your opinion extrinsic evidence is in general less reliable than the patent and its prosecution history in determining how to read claim terms, correct?

A. I mean I'm aware that that's the legal standard, yes. I mean I have no, I don't disagree with that.

Q. Okay, I just want to be sure we're clear because I'm not asking if you're aware it's a legal standard. I'm asking about your opinion, your opinion

in particular. So let me try my question again. Is it correct that in your opinion extrinsic evidence is, in general, less reliable than the patent and its prosecution history in determining how to read claim terms?

MR. HU: I'll object to that whole part that was the wind-up to what ended up being the question.

A. You said in general, right? And in general, I believe that's true, that's, that's fine. I can't say that, that there aren't, there isn't extrinsic evidence that sometimes might be particularly valuable. But in general, I believe that that's a fair statement.

Q. Now for this particular litigation, did you think about weighing the intrinsic and extrinsic evidence that you relied upon differently?

A. And by this particular -- so we were talking just a second ago about other litigations and now this litigation. We're talking about the

LATUDA® litigation right now when you said this litigation; is that right?

Q. That's right.

A. Okay. I mean, I mean I, I think inherently I would -- I used the '372 patent as the, as the primary source. And that I come to -- came to, you know, some conclusions that I then tried to substantiate with references that happened to be, you know, extrinsic evidence. The external references don't bear directly. In other words, the structures are not the same, the compounds are not the same, but the way of rendering the structures is the same.

And so I think to answer your question, I don't disagree that, in general, the patent is more important than, you know, than the references, so.

Q. And my question is a little different. So my question is for this particular case, did you think about weighing the intrinsic and extrinsic evidence differently?

MR. PREW: Objection, form.

MR. HU: Thank you.

A. I mean the only time that that would be important is if, as I understand it, is if the extrinsic evidence and the intrinsic evidence suggested different conclusions and then you have to decide which one is more important. But I find, I found them all to be supportive of the same general conclusion. And so I don't know that I actually put a weighting factor on any of them.

Q. So for this particular case you didn't put a weighting factor on the intrinsic evidence or the extrinsic evidence?

MR. HU: Objection, asked and answered.

A. I mean I did say that I viewed the patent as being the most important piece of the document. So there is inherently a weighting factor in that.

Q. Can you -- did you -- did you put a weight and factor on the

A. Okay. Just in general terms. I mean most of this, of this type of work that I do, not all of it but most of it happens to be ANDA related and I'm aware of paragraph 4 certifications and things like that. I don't know details, legal details of them but I'm aware of what they are.

Q. And what's your general understanding as to what a paragraph 4 notice letter contains?

A. Again, this is my understanding but it's a, you know, a letter informing the branded drug that they intend to market a generic version thereof and that they either, that they don't infringe for particular reasons or that they do infringe and they intend to, you know, fight, they don't believe the patent is valid or something like that, sort of the, the basis for how things are going to move forward.

Q. Okay.

A. Again, that's just a general

impression and...

Q. Right, right. And in your work for patent litigations, you worked on behalf of innovative or ethical companies as well as on behalf of generic drug manufacturers, correct?

A. That's correct, yes.

Q. And are these paragraph 4 notice letters, are there serious statements involved?

MR. HU: Objection to the form of the question.

A. I mean my guess is, I mean they're, yes, they're serious. They're legal documents and they're, yes, they're, they're serious.

Q. And they could potentially lead to litigation, correct?

A. That I don't know.

Q. Oh.

A. But, you know, I'll, I'll accept your, your statement that they could be.

Q. Got it. Have you ever viewed

any notice letters in this case, other than the one that I provided to you and you only took a look at it for just a few minutes?

A. In this case?

Q. Correct.

A. The answer is no.

Q. Okay.

(Whereupon Baldwin Exhibit 8 was marked for identification, paragraph 4 certification notice letter provided to plaintiffs by Teva.)

Q. I've had the court reporter mark as Baldwin Exhibit Number 8 a multipage document that I'd like for you to review.

MR. RATLIFF: And I just notice that at a break what we'll do, we'll go through the exhibits, counsel, and just indicate Dr. Baldwin's name. Because right now the labels just say exhibit 7. So just to avoid the confusion.

MR. HU: Could I make a suggestion? I think it would be a lot cleaner on the record and safer if you were to give a little bibliographic information about what the exhibit is when you mark it or when you first raise it if you've premarked it, just saying exhibit 8, I think it would be easier if you told us what it was. Okay, thanks.

MR. RATLIFF: Thanks for the suggestion, but that's not my practice.

MR. HU: I think it's clearer. Okay.

Q. Sir, have you seen this document before?

A. No, I have not.

Q. So I can represent to you that Baldwin Exhibit Number 8 is a paragraph 4 certification notice letter that was provided to plaintiffs by Teva, one of the companies who you're now engaged with

STEVEN WORTH BALDWIN

for this litigation.

A. Okay.

Q. And, sir, if you could turn your attention to page 20 of this document.

A. There don't seem to be page numbers.

Q. If you look towards the top of the document I believe there may be page numbers.

A. I see. No -- yes, I got it. I'm sorry. Well, no, there -- page 3 follows page 8.

Q. Let's see if I can help you. Okay, so I just put a tape flag, an orange tape flag on the document for page 20 and maybe what I'll ask you to do, I'll hand it to you with page 20 open, if you could just put a star, an asterisk on that page and then just put your name next to the star so it will be clear for the record.

MR. HU: This is solely for identification purposes?

STEVEN WORTH BALDWIN

MR. RATLIFF: Correct.

MR. HU: Thank you.

A. Anywhere in particular? Up by the flag? I mean --

Q. Anywhere of your choosing. And just put your, put your name so it's just indicated that this is the page 20 we're referring to.

A. You want me to write page 20?

Q. No, that's fine. Thank you.

A. Mm-hmm.

Q. So when you, when you read plaintiff's brief concerning claim construction --

A. Okay.

Q. -- did you understand that plaintiffs have asserted that each of the defendants have already agreed that Claim 14 includes lurasidone?

MR. HU: Objection to the form of the question.

A. I mean I, in that document, in the document I read, I saw statements to that effect, yes.

STEVEN WORTH BALDWIN

Q. Okay.

A. Yes.

Q. And after seeing that, did you review documents that plaintiffs were citing to concerning plaintiffs' assertion that defendants have already conceded that Claim 14 covers lurasidone?

MR. HU: Objection to the form of the question.

A. I reviewed no other documents, no.

Q. You weren't curious to see what was the basis for plaintiffs' statements in that regard?

A. I mean I did ask is this a document I should be reading and they said you don't need to.

Q. And did you ask why you don't need to read those documents?

A. No. I didn't because I assumed there's a strategy. I mean I don't, I just didn't worry about it.

Q. Right. Got it. Okay. So turning your attention to this page 20,

STEVEN WORTH BALDWIN

looking at the second paragraph, the first line that reads "Claim 14 of the '372 patent is the narrowest claim that covers lurasidone," do you see that?

A. I see that.

MR. HU: Objection. Mr. Ratliff, are you going to ask him about a document that he's never seen before and ask him to give, formulate opinions today based on a document, multipage document that he's never seen before, is that, because I think that's inappropriate?

MR. RATLIFF: Okay. Glad you think that.

Q. All right. So and you've never seen, seen this page before, sir?

A. No, I've never seen this page.

Q. And based upon your reading of that sentence, do you believe it to be a statement that Claim 14 of the '372 patent actually covers lurasidone?

MR. HU: Objection. This is

very unfair. Professor Baldwin is not here to formulate opinions on a document he's never seen before on a statement taken in isolation.

A. And I, I mean I'd feel -- I mean in reality this is a legal opinion right here. And I'm not capable of forming a, you know, a legal opinion. And so I mean I just don't have the training.

Q. Right. Oh, and sir I'm not asking you for a legal opinion. I want just your understanding as a scientist as to what this statement means?

MR. HU: Professor Baldwin, please read the whole document if you need to to have the context. I'm not going to let him answer it in the abstract like this. This is not appropriate.

MR. RATLIFF: On what basis?

MR. HU: It's not appropriate to examine on a document he's never seen before.

MR. RATLIFF: Not appropriate is not in the rules.

MR. HU: It's definite beyond the scope of his report which is where I was going. He's never seen it. Not part of his report. That's the point.

MR. RATLIFF: Okay.

Q. So Professor Baldwin, again just asking for your view, as a scientist, of this one incidence that reads "Claim 14 of the '372 patent is the narrowest claim that covers lurasidone and is addressed first for that reason." When you read that, as a scientist, is it your understanding that someone believes lurasidone is covered by Claim 14?

MR. HU: I have the same objections and same cautions for Professor Baldwin. If he needs time to read the whole document, he should take it.

A. Again, I don't -- I mean I see, I read, I see what it says. And,

you know, my problem is first just looking at it this way I don't agree. I don't agree with the statement. And so I'm not quite sure what you want me to do.

Q. Right.

A. Do you want me to say that I've read this and that I agree with it?

Q. No, not at all. So let me try it again because I thought I was clear. I understand your opinion, it's in your declaration and we've talked about it.

A. Sure.

MR. HU: Objection again to the wind up. Ask a question please.

Q. So I understand your opinion. So my question is very different. It's looking at this sentence that I just read, the one sentence, in your view as a scientist does it appear to you that at least the author of this document believes that lurasidone is covered by Claim 14?

MR. HU: Objection to form of the question and object to asking him to give opinions based on one sentence in a document he's never seen before.

A. Yeah, and I mean I know that's what it says. I don't agree, again I don't agree with it and I think I would have to read the entire thing to put it into context. And I'm, you know, I can do that. But I don't know why -- I mean I just don't understand why the, why the sentence is there, you know, what it's there for. I'm not prepared to answer your question.

Q. Right. But as you read it, it appears that someone is saying that lurasidone is covered by Claim 14, right?

MR. HU: Objection to the form of the question.

A. I mean that's, that's what it says. I mean, for instance, I'm not quite, you know, hundred percent sure what covers means, you know, as well. I

mean that's, that's a legal term with lots of nuances and everything else, I'm not prepared to, you no, I'm not prepared to deal with that.

Q. Right, right. And do you recall me asking you earlier if Claim 14 covered lurasidone, and you, do you recall ever having trouble with that question?

A. Before?

MR. HU: Objection to the form of the question.

A. Before? I said Claim 14 did not cover lurasidone.

Q. Okay. So you do understand what the word cover means?

A. Yeah, and I suspect that at that time I probably interpreted covers as includes or whatever. Here this is a legal term and I didn't write it and I'm, I don't know quite what to say here other than, other than I'm happy to read the whole, the whole thing. I'm not sure that I'd be able to answer the question

then. But I'm happy to do it.

Q. Okay. So what we'll do, we're going to have -- we will keep going. We will have a lunch break and feel free to read it over lunch and then I'll ask you the question again after lunch.

All right. So let's take a look at Baldwin Exhibit Number 7. This is the notice letter from Emcure that we talked about earlier.

A. Yes.

Q. Turning to page 17, and again the numbers are very faint so maybe I can, I can help you out if you hand that to me, sir.

A. No, I've got it. I can see your numbers on this one.

Q. Okay. And they're not my numbers, they're actually Emcure's numbers, just for clarification.

A. Okay, I think I'm there.

Q. And -- well before I ask you the question. No, let me just ask the question.

So turning your attention to the section 3 entitled Differences between the Prior Art and the Claimed Subject Matter, do you see that?

A. Yes.

Q. Okay. And do you see the second sentence beginning "More specifically,"?

A. Yes.

Q. Would you please read that to yourself and let me know when you're finished.

A. I think I've read it, yes.

Q. Okay. And in your reading of this sentence beginning "More specifically," is it your understanding from a scientific perspective, not a legal perspective, that the author of this document is saying that lurasidone is covered by Claim 14 of the '372 patent?

MR. HU: I have the same objections. It's not -- it's outside the scope of his

declaration and you're asking him to give opinions on the spot on a document that he's never seen and compounding that, it's a one specific sentence out of context, out of a -- in a very lengthy document.

A. This is --

MR. RATLIFF: You're speaking objections are noted.

A. "More specifically compound 1 of the '117"... okay, the '117 patent. What I can say, I'm not -- okay. Please ask -- could you ask your question again.

Q. Sure.

A. So.

Q. In reading that sentence, do you understand, from a scientific perspective, that the author is saying that the compound of Claim 14 includes lurasidone?

A. No, I don't. I don't, I don't see that at all. Okay. I mean compound 1, first of all, there's -- oh, I'm

looking at the structures here. Yeah, I -- more specifically, compound 1 of the '117 patent contains... oh, I see what you're saying.

MR. HU: Before you answer that, Professor Baldwin, I have the same objections as to the previous question.

A. So, yeah, I see the -- okay. So these structures are different but they have common, some common structural features and the point is that you're asking is that Claim 14, they've identified as including lurasidone.

Q. That's right.

A. That's what it says, yes.

Q. Okay. Sir, if we could turn to Baldwin Exhibit Number 4, which is a copy of your declaration.

A. Okay.

Q. Turning to page 11 of your declaration, and in particular looking at paragraph 27.

A. Okay.

Q. Are you there, sir?

A. Yes, I am.

Q. Now in paragraph 27 are you essentially making the point that a racemate is commonly represented by depicting one of its constituents enantiomers?

MR. HU: Objection to the form of the question.

A. I mean that's, yeah, that -- well, I'm pointing out that, that this author, Maitland, Maitland Jones, you know, says, says that. That when you're writing, when one writes chemical structures, that racemate is assumed unless there's an indication that it's not racemate.

Q. Would you agree that the depiction of one enantiomer does not always represent a racemate?

A. Yeah, when it's, when there's a clear indication that a, that a depiction isn't a racemate then it isn't. I mean if one says, you know, as I said

before, identifies this as the (+)-enantiomer or the (-)-enantiomer or the compound with a particular configuration, RR versus SS, something like that, then the assumption is that it is a racemate. So if there's not an indication, then that has, that's the starting point, that's your, that's your, you know, that's your reference point.

Q. What was my question?

A. We should ask the reporter.

Q. Do you remember?

A. Yes, the --

MR. HU: Objection, you're harassing the witness. Ask the question.

Q. Do you remember my question? I just want to be sure I'm not wasting your time, and getting responses to the questions I actually asked. Let me try it again.

MR. HU: Thank you.

Q. Would you agree that a depiction of one enantiomer does not

always represent a racemate?

MR. HU: Objection. That was asked and answered.

A. And I said, I would agree that that's the case if there's an indication to that effect.

Q. Okay. So you agree that the depiction of one enantiomer does not always represent a racemate?

MR. PREW: Objection, mischaracterizes his testimony.

MR. RATLIFF: And your speaking objections too? Come on, counsel, please.

A. With, with -- under the conditions that I said, yes, I agree.

Q. Okay, okay. For a patent claim, do you agree that a depiction of one enantiomer could represent the individual enantiomers, as well as equal and unequal mixtures of the enantiomers?

MR. HU: Objection to the form. What are we talking about? Are we talking about -- what patent

are we talking about?

A. If there's language in the patent that actually specifies that, then, yes, I agree. If there's not, then my original opinion holds.

Q. Got it. Okay. Now looking at paragraph 27, one of the first -- well in paragraph 27 the first document you cite is an excerpt from Jones, do you see that?

A. Yes.

Q. Is this a -- is this one of the documents that you found yourself?

A. Yes.

Q. Okay. And you agree that this document is intrinsic evidence?

A. Intrinsic evidence?

Q. Sorry, maybe I said it wrong. You believe that this document is extrinsic evidence?

A. Yes, I do.

Q. And you agree that this document was also not available to the person of ordinary skill in the art at

the time the July 5th, 1991 '372 application was filed?

A. Yes. I mean this was published later.

Q. Right.

A. But it certainly represents the way people had been looking at this, you know, drawing these structures for long before 1997.

Q. It's not prior art this document, '327, this patent, right?

MR. HU: Are you asking him for a legal opinion as to the legal status of this document?

Q. Sir, exhibit number 7 is not prior art, to your knowledge, to the '372 patent, correct?

MR. HU: Objection to the form.

A. Yes. I mean I pointed out that this is a 1997 article, that the patent we're talking early '90's for the, for the patent.

Q. And the second reference that

you cite, exhibit number 8, that's also an extrinsic source, correct?

A. That's correct.

Q. And that document was also not available to the person of ordinary skill in the art at the time of the July 5th, 1991 '372 patent application, correct?

A. That's correct.

Q. When you attached exhibit 7 to your report, did you check it carefully?

A. I'm not sure what you mean. I mean I pulled the book off my shelf. I read this section. I thought that it was relevant. So I'm not sure what you mean by checked it carefully.

Q. When you pulled the book, did you confirm that it was actually the second edition of the book as opposed to some other edition?

A. Oh. Okay so let me go back. Did I say -- what paragraph am I dealing with here?

Q. Paragraph 27.

A. That's right, thank you very

much.

Q. You're welcome.

A. Okay, you said, I'm sorry, you said second edition? Which one are we talking, are we talking -- this is the Jones?

Q. Right. So talking about the Jones.

A. Okay.

Q. So the question is, you have a copy of Jones on your shelf in your office; is that correct?

A. Yes.

Q. When you pulled Jones and decide to include it in your declaration, did you check to see in fact whether or not your Jones was the second edition or some other edition?

A. And, you know, I'm sure I did. If there's a typo there, then I didn't pick it up, pick up on it so I'm not sure.

Q. Okay.

A. I mean I copied the, you know,

the relevant early, you know, cover pages in there that list the edition and if that -- if I made a mistake, it's my apologies.

Q. Okay.

A. So I don't know whether I did or not because if I don't have the cover page in here to look at.

Q. And you didn't provide that cover page to us in your declaration, correct?

A. I provided the cover page to my, you know, to the attorneys and I didn't actually prepare the exhibits myself.

Q. Okay.

A. To send.

Q. Okay. At any rate, the text that you include from Jones, whether it's a second edition or some other edition, that would have not been something that a POSA, in 1991, would have read because it didn't exist, correct?

A. It didn't exist in 1991. But

there's nothing new here. This is the way people operated in 1991 and well before that.

Q. And that's not my question.

A. I know, I understand.

Q. A POSA would not have read this text in 1991, correct?

A. A POSA would not have read this text because it was still multiple years in advance, so.

Q. Understood. So now looking at this second reference, Vollhardt?

A. Vollhardt, yes.

Q. Do you also have a copy of Vollhardt on your shelf?

A. Yes, I do.

Q. Do you have multiple copies of Vollhardt on your shelf?

A. I have multiple copies, ie., not copies of the same edition, but multiple editions.

Q. Right. Do you know if there were prior editions of Vollhardt prior to the 2010 edition that you referred to in

your declaration?

A. I know, I mean I know that there were.

Q. And do you know if any editions of Vollhardt existed prior to July 5, 1991, which is the '372 patent application date that you refer to in your declaration?

A. Yes, so there's two authors on, for this book, it's Vollhardt and Schore, Neil Schore and there were several earlier, and I suspect that one of the early editions went, you know, was published before 1991. And then there was a single author book by Vollhardt prior to that where he was again the only author. And those editions go back, I think they go back into the early to mid '80's. I don't remember exactly when edition 1 came out.

Q. And this language that you cite from Vollhardt and Schore in paragraph 27 of your declaration, do you know if that language was included in any

of the prior editions of Vollhardt and Schore?

A. So I, I didn't have access personally to all of the early editions. I did check a couple of others and this language was not included.

Q. Okay. And is it your understanding that prior to July 5, 1991 the language that you cite from Vollhardt and Schore was not included in the earlier editions?

A. Yes, again, I haven't checked every edition but the editions that I checked, the answer is it was not included.

Q. Is it correct that as of July 5, 1991 the language that you cite from Vollhardt and Schore, the 6th edition, from 2010, some nearly 20 years later than the July 5, 1991 application, was not available to the person of ordinary skill in the art?

MR. HU: Excuse me, could I hear that question back.

(The requested portion of the record was read.)

MR. HU: Thank you.

A. Yes, that specific language was not available. The ideas were widely in practice.

Q. And when we look at the specific language that you cite from Vollhardt and Schore, it refers to the writing of a chemical equation when racemates are involved; is that correct?

A. That's correct, yes.

Q. Claim 14 of the '372 patent, does it recite a chemical equation?

A. No, it does not. It recites a specific structure.

Q. Now turning to paragraph 28 of your declaration. Do you have that, sir?

A. Yes, I do.

Q. In paragraph 28 you list 5 other documents that are extrinsic sources to the '372 patent; is that correct?

A. That's correct.

Q. And essentially your point here is that these publications use an enantiomer to indicate a racemate?

A. That's correct.

MR. HU: Mr. Ratliff, while there's a pause, what are your intention about a lunch break? I don't know if Professor Baldwin is getting hungry but it is almost 12:30. Can we just discuss that briefly to see what the schedule is for the rest of the day?

MR. RATLIFF: Sure.

Q. Professor Baldwin it's your day so it's up to you whenever you want to take lunch.

MR. HU: I guess in part it depends on how much, how long you want to go because he may want to just keep going. I don't know. I'm not speaking for him.

Q. Unless you want to have a very late lunch, then I suggest that you take lunch sooner than later. I'm not

finishing before -- any time soon.

A. Yes, I mean I'm not going to faint dead away at any point in the near future.

Q. Okay.

A. But I would at some point like lunch.

Q. Yes, me too.

A. So.

Q. Okay. So just let us know and I'll let you know. I do have it on the top of my mind. I'm sensitive of the time.

A. May I -- I think I might want to clarify something in the, you know, the question and answer that you just did. Can we go back and talk about the structure? Remember you talked about the structure and a structure representing a racemic mixture versus an enantiomer and I want to make sure I didn't misspeak.

Q. Well you're going to be given an opportunity to take a look at the transcript.

MR. HU: Let's do it now. That's not fair. He wants to clarify an answer he gave. Please read it back. That's not fair.

MR. RATLIFF: Please read what back?

MR. HU: He asked for a question and answer to be read back. That's only fair.

MR. RATLIFF: Do you know what question, counsel?

MR. HU: No. But Professor Baldwin has just asked.

Q. Do you know what question, Mr. -- Dr. Baldwin?

A. You asked --

Q. Is it professor or doctor?

A. Yes.

MR. HU: Both, but.

A. You know, you asked a question about relating to the fact that -- the Vollhardt textbook talked about writing structures as part of chemical reactions. But that the structure -- that Claim 14

instructions to determine whether or not your preference of calling it a racemic mixture is correct?

A. Well, first of all, is this showing up as, for instance, in a patent claim? I mean --

Q. Yes.

A. If it's part of a patent, then I would certainly go to the specification.

Q. Okay.

A. If it's part of a journal article, I would read the journal article. I mean my assumption would be racemic. And then I would read the journal article to see where it came from and see if in fact it was actually, you know, a single enantiomer.

Q. Okay.

A. But, you know, the initial assignment would be as a racemic mixture.

MR. RATLIFF: I'd like the court reporter to mark as Baldwin Exhibit Number 11 a multipage

document.

(Whereupon Baldwin Exhibit 11 was marked for identification, copy of U.S. Patent 4,681,893.)

Q. Professor Baldwin, I just handed you exhibit number 11 which I can represent is a copy of U.S. Patent 4,681,893. And if you could turn your attention to column 16 of this patent.

MR. HU: You know, I'm going to object to this. This isn't in his, in his declaration as far as I know. And we've spent a lot of time giving you a lot of latitude on subjects that have nothing to do with the declaration. We've been really very patient. And you're certainly entitled to explore everything about his declaration. But to give him documents he hasn't seen and ask him all kinds of questions about things that he's looking at for the first time is really not appropriate. Are you

going to be doing this a lot? Because I'm seriously considering stopping this. So can you answer the question?

MR. RATLIFF: I'm not being deposed today. I don't answer your questions.

MR. HU: This is just an inquiry between counsel about the scope of the deposition. It's perfectly appropriate.

MR. RATLIFF: I'm asking questions that are appropriate.

Q. Professor Baldwin --

MR. HU: All right, let's see where this goes.

MR. RATLIFF: Please.

MR. HU: I think you are really pushing. You're way past the boundaries of what's appropriate.

Q. Professor Baldwin, if you could turn to columns 15 and 16. I think you're there.

A. I'm there.

Q. I'd like you to turn your attention to claim 1. And you should see within claim 1 a structure depicted. Do you see that?

A. Yes, I do.

Q. And that's the same structure that I provided you in Baldwin Exhibit Number 10.

A. Yes, it is.

Q. And could you review claim 1 and anything else in the patent that you wish and let me know whether or not you think the structure depicted in claim 1 represents a series of molecules that are racemic mixtures, or represents an enantiomer, or represents something else?

MR. HU: Really? Are you really asking him to read this patent that he's never seen now to give an opinion on this, when it's not in his declaration?

Professor Baldwin, why don't you read the whole thing, please,

before you answer this.

I tell you this. I'll give you this one. You can ask this. But after this, I think we may instruct him not to answer these. This is, this is so far beyond what's in the declaration.

Q. Go ahead and read it, sir.

A. Yes, I mean this is --

Q. Let me ask you the question first. Do you need to read the specification to answer my question?

A. Well, again, it's going to be -- by the way, is this something relevant that I need to worry about, this ex-parte examination thing? I mean is that -- I mean you included it. I just want to know if this is something I have to be concerned about.

Q. I included it for completeness because it's part of the patent.

MR. HU: Professor Baldwin, read everything.

Q. So the question pending --

MR. HU: I'm going to make a suggestion. It's a long document. Professor Baldwin, would you feel more comfortable going to a room by yourself? We'll sit here and wait for you to come back so you don't sit here with everybody watching you.

Q. Before you're there, the question is first, do you feel that you need to read the patent specification to answer my question as to whether or not the structure depicted in claim 1 of this patent represents a series of racemic mixtures, a series of enantiomers, or something else?

A. I mean as I look at the structure, my -- I would -- and again in the upper, very upper right there, is that something there that I -- is that an I? That's not anything like a plus or a minus or anything like that, is it? You see in the very upper right portion of the column, you see a little line. I

don't know what that is.

Q. I see it. I don't know what it is either.

A. Or an l. So if that were a small l I would say this is probably a single enantiomer.

Q. Okay.

A. If that is not anything significant, then I would say my initial reaction, my reaction would be that this is a racemic mixture.

Q. Okay. And do you believe that it's possible, and I recognize that you haven't read the patent specification, but do you believe it's possible that the structure depicted in claim 1 could actually be representative of racemic mixtures, enantiomers, as well as unequal and equal mixtures of the enantiomers?

A. I mean if there's -- if there then is language to that effect, then yes. But in the absence of that kind of designation, the answer is no. I mean just quickly I notice that claim 5 in

fact is racemic materials, you know, as I look at this.

And I haven't gotten any further so I don't seem to see any suggestion, just on the top, off the top of my head here, I don't see any suggestion that it's a -- that non-racemic materials are included in the claims. But without taking time, I'm not going to hang my hat on that.

MR. HU: Do you want him to read it?

A. I mean as I look at the compounds, I mean I know these things are, they look like they're probably, you know, anti-cholesterol drugs would be my best guess. And I know that those drugs are single enantiomers. And so but there's no information that I see here to that effect, so.

Q. When you say see here, what are you referring to?

A. Well I'm looking at claim 1. I look at claim 1 here and I see what I

would say is a racemic mixture. There's relative stereochemistry, you know, shown between the two stereogenic atoms and so the hydroxyl and that parole side chain are trans to one another but they could be trans this way or trans that way according to this structure.

Q. And so to confirm whether or not the structure depicted in claim 1 is actually representative of racemic mixtures or something else, you would have to consult the patent specification; is that your testimony?

A. Well, I mean I certainly also, I'd also look at the rest of the claims and then see if, you know, this is an independent claim, if there were dependent claims that said a structure according to claim 1 in which the material is the, you know, (+)-enantiomer, something like that. And then also the text part of the specification.

Q. Right. And from your

perspective, is the structure depicted in claim 1 -- let me try this again.

From your perspective is the question that -- strike that.

From your perspective, the structure that's depicted in claim 1, are you considering whether or not it could be a racemic mixture, or an enantiomer, or are you considering the possibility that it could be representative of all of those things, meaning specifically the individual enantiomers, as well as equal and unequal mixtures of enantiomers?

MR. PREW: Objection, form.

A. I mean let me -- it is certainly possible for this. And again, we're looking at a large collection of molecules, but let's just zero in on one representative one. It certainly is possible for that to exist as a racemic mixture or for it to exist as either an enantiomer. And it's possible that it would -- it could exist as a mixture but non-racemic of those two compounds. But

the starting point, looking at this, with no additional guidance, is that this is a racemic mixture.

Q. Is it possible that the structure can actually represent the individual enantiomers, as well as equal and unequal mixtures of those enantiomers, all of those things, is that possible?

A. Yes. If there's specific language to that effect, then the answer is yes.

Q. If you could turn your attention to column number 3 of Baldwin Exhibit Number 11.

A. Okay.

Q. And, sir, if you could please read to yourself the first two paragraphs of the detailed description.

A. Okay.

Q. And let me know when you're finished.

MR. HU: Professor Baldwin, if you need any, to look at anything

else to answer his question feel free to do so. You're not limited to only the portions that are pointed to.

Again, he hasn't seen this document. It's not in his report.

A. And I haven't heard a question yet, so.

Q. Excuse me, Professor Baldwin, you haven't heard what?

A. I said you asked me to read these and so I don't know what the question is going to be, right, so that's all I was saying.

Q. Okay.

A. Yeah. Okay, the first two paragraphs and I'd say there's a little bit of ambiguity in this paragraph, so.

Q. Which paragraph are you referring to?

A. Well in the second paragraph that you asked me to read, they talk about R-cis and S-cis, et cetera. They're not -- the R and the S are

associated with the stereogenic atoms and they're not saying which stereogenic atom they're talking about, what the reference point is. And so I'm a little unclear.

Q. Anything else?

A. Unless they're both -- and I'd have to do the -- I'd have to do the -- only the trans -- wait a minute, R-cis, R-trans and S-trans. And again, it may be possible that -- I don't think so. I don't know. I don't see -- okay, so I read it but I'd say there is some ambiguity in that, in that paragraph.

Q. And the ambiguity as to what?

A. Well, there's a stereochemical descriptor, S versus R, and there's like -- it says, for instance, in line 50, this asymmetry gives rise to four possible isomers, two of which are the R-cis and S-cis-isomers, but we don't, we don't know which is the R-carbon and which is the S-carbon. And so I'm not quite, I just don't know, you know, I don't know what the reference point is

here unless there's something that came earlier which I don't know.

Q. Fair enough. Do you think anything in the second paragraph that you read provides you information as to whether or not the structure in claim 1 would encompass racemic mixtures, as well as individual enantiomers, as well as unequal mixtures of the enantiomers?

MR. HU: Objection to the form.

MR. PREW: Objection.

MR. HU: I'm also objecting to the fact you're not giving him a chance to read the whole thing. He's bent over backwards to be cooperative. I think you should give him a chance to read the whole thing.

MR. RATLIFF: I'm not sure what deposition you're at. I didn't tell him he can't look at anything.

A. I suspect that in that second

paragraph that -- of two which are the R-trans and S-trans-isomers. And I guess I have to ask another question. Is this the reference structure up here at the top or are we talking -- I mean because this is a different structure that's over on claim 1.

Q. Right.

A. So --

Q. And I'm referring to the structure that's in claim 1.

A. I mean the language here, so the R-trans is going to be -- okay, they've restricted the, or the conversation to R-trans and S-trans-isomers. My -- it would appear that those two are enantiomers. And it doesn't say whether they're going to use one versus the other or a racemic mixture there, okay.

Q. Does it say the other possibility, that it could be both an enantiomers, racemic mixtures, as well as unequal mixtures of the enantiomers?

A. It doesn't --

MR. PREW: Objection to the form. You can read the document, Dr. Baldwin, if you need to answer the question. He's pointing you to two paragraphs. It's a long document.

A. I think I better go through it a bit more because, you know, I -- this doesn't -- this identifies those two enantiomers. It doesn't say anything about whether only one, only the other, 50/50 mixture, non-50/50 mixtures. It just says those are the compounds they are interested in.

Q. And that's all I'm asking for, your understanding.

A. I mean just based on that.

Q. Correct, just based on that. Just based upon that, to you it doesn't provide any information as to whether or not the structure in claim 1 was intended to cover racemic mixtures, individual enantiomers, either in their equal or

unequal parts, correct?

MR. PREW: Same objections.

A. Yes, there's no instruction there at all. So again, what this -- what one would have to do looking at, at claim 1 is that absent specific instruction, the starting point is that this is a racemic mixture.

Q. Right. And that second paragraph that you read is, in your view, irrelevant to that question as to whether or not the structure in compound 1 would encompass racemic mixtures as well as individual enantiomers in their equal and unequal parts?

MR. HU: Objection, that mischaracterizes his testimony. You're taking one paragraph in isolation and then mischaracterizing what he said.

A. In my -- claims generally build on one another and you start off with the general and you get more specific. This is in claim 1 and this is

the general situation. And I would say you start off with a normal interpretation of that, which is that it's a racemic mixture.

It doesn't mean that if there is, you know, further indication somewhere else that in fact we're going to deal with single enantiomers or that we're going to deal with two to one mixtures, I mean that's a possibility. But as drawn, this structure, the starting point is that this is a racemic mixture until there's instructions to the contrary.

Q. Okay. And I think I understand your position on that. So my question is a little bit different. It's whether if the second paragraph, in your view, provides any further instruction, information, enlightenment, knowledge as to whether or not the structure in claim 1 was intended to cover racemic mixtures as well as individual enantiomers in their equal and unequal parts?

MR. HU: I have the same objections as before, taking one thing out of context without giving him the opportunity to look at the whole patent.

MR. RATLIFF: I'll remember the speaking objection there.

A. I mean I think I've answered this to the best, to the best of my ability. I think it's clear that they are going to be interested in at least individual enantiomers. But I don't believe that claim 1 identifies that this is, these are individual enantiomers.

Q. And do you believe that that second paragraph provides any instruction or information as to whether or not claim 1 encompasses individual enantiomers?

A. No, I don't believe, I don't believe it does.

Q. Okay.

A. Okay?

Q. Thank you. So if you could turn to your declaration which is Baldwin

Exhibit Number 4. And turning to paragraph 29.

A. Okay.

Q. And in this paragraph you refer to a document that was published in July of 2011; is that correct?

A. Yes, I do.

Q. Is this a document that you found in your search for information that was relevant to the case, or is it a document that was provided to you for your consideration?

A. It was provided to me.

Q. And based upon reviewing the document you feel that it's appropriate to rely upon it to provide your opinion as to the proper interpretation of Claim 14?

MR. PREW: Objection, form.

A. I would say that it is, that the way the information is presented in this 993 document, you know, is consistent with the way I have described what structures mean, that is racemic

opinion and your opinion only, do you consider Compound 101 a single compound or not at single compound?

MR. HU: Objection, it's been asked and answered.

A. I mean there is no question but that it, there is a mixture, equal molar mixture of two enantiomers that behaves as if it's a single compound.

Q. Did you do any experimental work to follow the synthesis process for Compound 101, as described in '372 patent, to confirm whether or not that compound is actually a racemic mixture as you believe?

A. No, I did no experimental work.

Q. In paragraph 38 of your declaration, you explain that compounds 102, 103, 104 and 105 of the '372 patent are set forth in the specification of that patent; is that correct?

A. You said the preparation of those compounds? The preparation is

described --

Q. Let me try my question again. In paragraph 38 of your declaration you explain that compounds of 102, 103, 104 and 105 are described in the '372 patent specification?

A. Yes.

Q. Are they set forth as examples or exemplary compounds of the invention?

A. Well, you know, it's called, yes, example 1 B, example 1 C, example 1 D and example 1 E for those four materials.

Q. And are those four materials in the examples described as referred embodiments of the invention?

A. Specifically as preferred embodiments? I mean the fact that they show up as examples means, probably suggests that they are compounds that they want you to take particular notice of. I would say that they are preferred embodiments, yes.

Q. And would you say that they're

also compounds that the inventors intended to cover in their claims?

MR. PREW: Objection, form.

MR. HU: That calls for speculation.

A. I mean again, I have no idea what they, you know, what they intended to do, so. I just don't know.

Q. In reading the patent application -- strike that.

In reading the patent specification, you didn't gain any understanding as to what the inventors intended to include as part of their invention?

A. Well I mean I know what they were, you know, what they were looking for. They were looking for effective antipsychotic drugs that had a side effect profile that was favorable. So they were trying to identify compounds that did that.

Q. And did you read the '372 patent specification carefully?

A. Yes.

Q. And when you read it, did you come to any understanding as to what the inventors said their invention involved, specifically with respect to enantiomers?

A. I don't recall any specific language about enantiomers.

Q. Do you recall any specific language, when you carefully read the '372 patent, as to whether the invention involved isomers and mixtures of isomers?

A. I mean I'm not quite sure. I mean certainly at the very beginning, ie., for instance, column 4, they, they talk about, you know, in terms of stereoisomers, they do like in line 51 can have stereo and optical isomers and things like that. So that's certainly there, you know, as it refers to this huge collection of compounds defined above it right there. So I mean they talk about that.

Now in specific case are you, are you talking?

A. No, none.
Q. Now if you could turn your attention to your declaration, which I believe you have in front of you, and in particular looking at paragraph 43. Do you have that, sir?
A. Yes, I do.
Q. And in paragraph 30 -- strike that. In paragraph 43 you state that defendants proposed construction of the claim term, the imide compound of the formula, and you have a structure depicted at the top of 17 is consistent with how a person of ordinary skill would construe the phrase in the context of the '372 patent, and its file history?
A. Yes.
Q. And I notice when you make that statement you leave out the extrinsic sources that you relied upon in your declaration, correct?
A. I'm not sure, what do you mean that I left --
Q. Sure, sure. So when we look

at paragraph 43, the last sentence, you say based upon your personal knowledge, education and experience, that a person of ordinary skill in the art would construe the phrase consistent with the defendants' proposed construction in the context of the '372 patent, and its file history?
A. Yes.
Q. And I just want to be sure we're clear. When you render the opinion that defendants' proposed construction is consistent with yours, are you relying upon the extrinsic sources that you cite in your report, or not?
A. Yes, they're consistent. Yes, it's a consistent picture.
Q. So you are in fact --
A. Yes.
Q. -- relying upon --
A. Yes.
Q. -- extrinsic sources?
A. Yes.
Q. Do you agree that you cite

more extrinsic sources in support of your proposed construction than -- strike that.
Do you agree that you cite more extrinsic sources --
MR. HU: Objection.
Q. -- for your proposed construction -- -
MR. HU: Objection to form.
Q. -- as opposed to intrinsic sources?
A. Yes, there's a limited number of intrinsic sources so I do, yes.
Q. And is it correct that the only claim term that you plan to render opinion with respect to is provided in paragraph 43 of your declaration?
A. In 43, yes, that's the only one I was asked to consider, yes.
Q. Okay. And that's the only one you expect to provide testimony to the court regarding, correct?
A. I haven't heard -- I haven't been asked to consider any other claim

terms so I would assume so. I don't know if anything will happen after this, but.
MR. RATLIFF: I'd like the court to mark as Baldwin Exhibit Number 12 a multipage document.
(Whereupon Baldwin Exhibit 12 was marked for identification, copy of the declaration of Dr. Steven G. Davies.)
Q. Professor Baldwin, the court reporter has just handed you Baldwin Exhibit Number 12 which is a copy of the declaration of Dr. Steven G. Davies.
A. Yes.
Q. Can you please just take a look at this and let me know if you've seen Dr. Davies' declaration before?
A. Yes, I have.
Q. When did you see it?
A. Well, not long after I submitted my declaration so I don't know the exact date but it's within the last month is probably when I saw it.
Q. Okay. And are you planning to

provide any formal response to Dr. Davies' declaration in the form of a rebuttal declaration?

A. I'm not aware of any plans to do that, no.

Q. Okay. When you -- did you examine Dr. Davies' declaration carefully?

A. Yes, I read it quite carefully, yes.

Q. When you read Dr. Davies' declaration, did you find any aspects of it in which you have disagreement?

A. I mean, you know, his, his conclusion is, is that Claim 14 covers racemic mixtures, individual enantiomers and basically any mixture thereof. And, you know, I don't agree with that. So I mean without going through it again, I mean it's been a while since I read it, I can't, I can't, you know, I don't want to say there's no other place I disagree, but that's his bottom line which is clearly not consistent with my bottom

line, so.

Q. Okay. And so you have the declaration in front of you. Can you point me to other places that you have a disagreement with Dr. Davies' opinions?

A. Just give me a sec here.

Q. Sure.

A. I mean I, you know, it's hard, but that's certainly the big one where we disagree on, you know, the reason that we're here. You know in his paragraph 44, for instance, he says that he doesn't believe that the cited, that the provided references provide any information that would impact a person of ordinary skills understanding of Claim 14.

And I would say that if, you know, the person of ordinary skill was looking at a particular structure and saying that it was an enantiomer, he would find those, most, many of those references being consistent with that structure. But I, I don't know what else to say here. I mean do you have a

particular place that you'd like to, like me to --

Q. In your last opinion that you just provided me, or last response, are you familiar with the references cited by the defendants in exhibit E -- sorry, strike that. Are you familiar with the references cited by the defendants in exhibit A of the joint claim construction and prehearing statement?

A. Oh, wait a minute, I may have mis- -- yeah, I may have misspoken. I don't know actually. I don't know that I am, to tell you the truth. I just -- it's getting late.

Q. Okay. And as you were responding to my question previously, you were thinking about the extrinsic sources that were cited in your declaration?

A. Yes, and of course he hadn't seen my declaration, so that's right.

Q. Right. And we've already established that some of the extrinsic sources that you cite in your declaration

hadn't even existed as of the time of July 5, 1991 for the person of ordinary skill in the art?

A. That's correct.

Q. To even review?

A. That's correct.

Q. So I don't know, I don't have anything specific. But, you know, I have the opportunity to ask you questions here today and so if you do have any other disagreements with Dr. Davies opinions, I kindly ask for you to let me know. And we can go through it, you know, paragraph by paragraph if you want. This is just, this is just the opportunity that I have and I have to ask.

A. No, I mean the big deal is, is that, you know, we disagree on what Claim 14 says. So I disagree with his interpretation. I'm sure he disagrees with my interpretation. But, you know, I don't see anything -- lurasidone. I mean a lot of this is, you know, is descriptive and I off the top, just

looking at this right now, I don't have any additional disagreements with him that I can see. It doesn't mean that they aren't there. I just don't see them. I'm not holding anything back.

Q. Okay.

A. Okay.

Q. And that's fair. I just have to ask the question because we can't be in a situation where you show up at court and you say, ah-ha, paragraph 55.

A. Gotcha.

Q. Right, that's all. Maybe if there's nothing that jumps out to you --

A. Yeah.

Q. -- when you read it or sitting here today, if that's the case just let me know?

A. There's nothing right now that, that I see. Now of course I've made notes on it and things like that which I don't have here.

Q. Okay.

A. And, you know, that could

refresh my memory. But I don't see any going through here. I'm not trying to be cute or coy. I simply don't see anything other than the major disagreement that we have.

Q. The big picture?

A. That's correct.

Q. The ultimate interpretation of the claim?

A. That's correct.

Q. And when you first reviewed Dr. Davies' declaration and then you made your notes, did -- was there something that, anything that stuck out in your mind as, ah-ha, this is a big disagreement or was it really just ultimate disagreement as to what the proper interpretation of the claim was?

A. It's, you know, it's the latter. His declaration to a large extent is descriptive and basically describes what's in the patent and then comes to a conclusion.

Q. Okay.

A. And I disagree with his conclusion.

Q. Okay.

A. Okay?

Q. Okay. And did you make a lot of notes?

A. No, these are more like put lines next to something to remind me to read that again, you know, at some point or I thought this was interesting. I didn't make, you know, handwritten. I didn't write words.

Q. You didn't write he's wrong, how could he possibly do that, say that?

A. For the following reason, no, I didn't.

Q. Okay, fair enough. Just want to be sure.

Do you know of Dr. Davies?

A. I'm aware, yes, I'm aware of Dr. Davies. I've heard, I've heard of him. I have just, you know, just scientific reputation.

Q. And have you met Dr. Davies?

A. I don't believe so. It's possible at some conferences or something like that, but I don't recall, you know, having met him.

Q. And when you say that you're aware of Dr. Davies by scientific reputation, what do you mean?

A. Well we publish, you know, similar work, synthetic organic chemistry. We make single enantiomers, et cetera. So I've read some of his papers. You know, just, just -- he's a, you know, he's a member of the community that I, that I move in and so it's reasonable that, and Oxford is a reputable place and I have other, I've had other friends. I had a postdoc at Oxford recently, so.

Q. Would you say that Dr. Davies has a good reputation in the field?

A. Yes. Oh, yes.

MR. RATLIFF: I'd like the court reporter to mark a multipage document as Baldwin Exhibit Number

13.

(Whereupon Baldwin Exhibit 13 was marked for identification, Opening brief in support of the plaintiff's claim construction in this litigation.)

Q. Professor Baldwin, have you seen Baldwin exhibit 13 before?

A. Yes, I have.

Q. Was this document provided to you by counsel?

A. Yes, it was.

Q. And I can represent to you it's a copy of the opening brief in support of the plaintiffs' claim construction in this litigation.

A. Just a minute.

Q. I'm representing it to you. You can disagree with it, that's fine.

A. No, no. I've seen this, yes.

Q. And similar to Dr. -- similar to when you reviewed Dr. Davies' declaration, did you also make handwritten notes on this document,

Baldwin Exhibit Number 13?

A. Probably not. I'm not sure. I was more interested in, not interested in, but it was more relevant, Dr. Davies. I mean I read this because it's, it's -- that's my job. I didn't make any serious notes. I may have put a note or a question mark or something like that somewhere, but.

Q. But nothing like that's wrong, how could they possibly say that?

A. No.

Q. When you read -- strike that. When you read Baldwin Exhibit Number 13, does anything come to mind as you having a major disagreement what was said in Baldwin Exhibit Number 13?

A. Well of course some of this I hadn't, I hadn't seen before. I hadn't seen paragraph 4 certifications that they talk about in here, you know, that kind of thing. And I'd say the -- once again they come to a conclusion about what Claim 14 means that's at odds with my

conclusion, and that's the, that's the big, you know, the big deal, the big point.

Q. When you read Baldwin Exhibit Number 13, were there any other disagreements that come to mind sitting here today or when you reviewed it that you had with its content?

A. And again when I'm reading this I'm reading it from a scientific point of view. So there's a lot of legal comments in here that I don't have the expertise to comment on. But I'd say that, you know, that scientifically it's, the issue is just the bottom line at the end.

Q. Okay. Is it your understanding that construing a patent claim involves a legal analysis?

A. Well it's, you know, I -- I mean a patent is a legal document so the claims are legal documents and so I think there's certain, to a certain extent, the answer is yes. But there's also science

built into at least some of the, some of the claims and so I'd say it's a combination, you know, of the two.

Q. Okay. And when you think about the claim construction process, do you give a weight to the legal aspects of the process versus the so-called scientific aspects of the process?

MR. PREW: Objection to form.

A. I mean my -- that's impossible for me to do. I mean I know the science. I'm an expert in the science. I'm barely conversant in the legal side. And so I look at it from the point of view of the science and I, and I provide my opinions. And my feeling is that it's up to the attorneys to filter that through, you know, the legal filter that puts these things into their right legal context, and so I'm looking at it from a scientific point of view.

Q. Okay. And when you engage in the claim construction process, do you ever review cases, court decisions?

EXHIBIT 11

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY
----------X
SUMITOMO DAINIPPON PHARMA CO., LTD. And SUNOVION PHARMACEUTICALS INC.,

PLAINTIFF,

-against- Civil Action No: 15-280 Civil Action No: 15-281 Civil Action No: 15-6401

EMCURE PHARMACEUTICALS USA, INC. and EMCURE PHARMACEUTICALS LTD.,

DEFENDANTS.
----------X

DATE: July 21, 2016

TIME: 9:10 A.M.

VIDEOTAPED DEPOSITION of the Nonparty witness, PROFESSOR STEPHEN G. DAVIES, taken by the Defendants, pursuant to a Notice and to the Federal Rules of Civil Procedure, held at the offices of Paul Hastings LLP, 200 Park Avenue, New York, New York 10166, before Norah Colton, CM, a Notary Public of the State of New York.

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* * *

F E D E R A L S T I P U L A T I O N S

IT IS HEREBY STIPULATED AND AGREED by and between the counsel for the respective parties herein that the sealing, filing and certification of the within deposition be waived; that the original of the deposition may be signed and sworn to by the witness before anyone authorized to administer an oath, with the same effect as if signed before a Judge of the Court; that an unsigned copy of the deposition may be used with the same force and effect as if signed by the witness, 30 days after service of the original & 1 copy of same upon counsel for the witness.

IT IS FURTHER STIPULATED AND AGREED that all objections except as to form, are reserved to the time of trial.

* * * *

THE VIDEOGRAPHER: This is tape 1. We are now on the record. The time is 9:10 A.M. Today is Thursday, July 21, 2016. This is the opening of the deposition of Stephen Davies in the matter of Sumitomo Dainippon Pharma Co., Ltd., et al. versus Emcure Pharmaceuticals USA, Inc., et al.

This deposition is being held at the offices of Paul Hastings, LLP located at 200 Park Avenue, New York, New York.

The Court Reporter is Norah Colton with Diamond Reporting & Legal Video. I am the legal videographer, Alejandro Lazare, also with Diamond Reporting & Legal Video.

Will Counsel please introduce themselves and state whom they represent.

MR. RATLIFF: Preston Ratliff from the Paul Hastings law firm in New York on behalf of the Plaintiffs

and also on behalf of the witness. And here with me today is Imtiaz Yakub also from the Paul Hastings law firm. We also have Michelle Flores from Sunovion. And I'll let a summer associate of the parties involved introduce himself.

MR. HWANG: I'm Frank Hwang. I'm a summer associate here at Paul Hastings. I go to currently -- I currently go to Michigan Law School.

MR. HU: Thanks. Chris Hu, Blank Rome, for Defendant Emcure, and with me is Jay Lessler, also from Blank Rome.

MR. GUERRIERO: Salvatore Guerriero and Pei-Ru Wey of Cesar Rivise on behalf of InvaGen Pharmaceuticals.

MS. HARDMAN: Cynthia Hardman of Goodman Proctor for the Teva Defendants.

THE VIDEOGRAPHER: Will the Court Reporter please swear in the

witness.

S T E P H E N G. D A V I E S, called as a witness, having been first duly sworn by a Notary Public of the State of New York, was examined and testified as follows:

EXAMINATION BY

MR. HU:

Q. Good morning.

A. Good morning.

Q. What is your preferred form of address? Doctor, Professor, Mr.?

A. It doesn't matter to me. Doctor, if you wish.

Q. All right. Thank you. Could you state your full name, please?

A. Steven Graham Davies.

Q. And where do you reside?

A. Seven Apsley Road, Oxford, U.K.

Q. And what is your present profession?

A. I am the Waynflete Professor of Organic Chemistry in the University of Oxford in the United kingdom.

Q. Do you have any other

professional responsibilities in addition to being a professor at Oxford?

A. I have many other responsibilities.

Q. Can you identify those, please?

A. I am the director of a number of companies. I'm an editor of a chemistry journal. That's all that comes to mind at the moment.

Q. Thank you. What are -- what's the nature of the business of the companies of which you're a director? Just generally.

A. They're to -- they're to do with the drug discovery and medicinal chemistry in general. I also have a publishing company, and I have a personal company, consulting company.

Q. Are you here today through the personal consulting company?

A. I don't understand what you mean by "through the personal consulting" --

Q. We'll get to that. When were

S. G. DAVIES

Q. In paragraph 43 of your Declaration you said that, and I will quote, "I have reviewed the prosecution file history of the 372 Patent and am not aware of any statements that would have been inconsistent with a person of ordinary skill, understanding of Claim 14 as I have discussed above."

Do you stand by that statement today?

A. I believe so, yes.

MR. HU: Okay. I don't have any more questions.

InvaGen and Teva?

MS. LAMBERT HARDMAN: No.

MR. GUERRIERO: No further questions.

MR. RATLIFF: Alright. Let's take a break?

THE VIDEOGRAPHER: We are now off the record. The time is 9:56 A.M.

(Whereupon, a short recess was taken.)

S. G. DAVIES

THE VIDEOGRAPHER: This is tape 1 of the deposition of Stephen Davies. We are now on the record. The time is 10:03 A.M.

EXAMINATION BY
MR. RATLIFF:

Q. Doctor, I have a few questions for you.

MR. RATLIFF: I'd like the Court Reporter to mark as Davies Exhibit No. 2 a multipage document that I'll represent is a copy of Dr. Baldwin's Declaration submitted in this case dated June 15, 2016 with appended to the Declaration the 14 exhibits to Dr. Baldwin's Declaration.

MR. HU: I will object to this because I think it's -- think. I know it's beyond the scope of the direct. We did not show him Dr. Baldwin's -- Professor Baldwin's Declaration. We did not examine him on it.

MR. RATLIFF II: You can finish

S. G. DAVIES

marking the Exhibit.

(Whereupon, the aforementioned Declaration of Steven Worth Baldwin, Ph.D, was marked as Davies Exhibit 2 for identification as of this date by the Reporter.)

Q. Doctor, I just handed before you a copy of what has been marked as Davies Exhibit No. 2. Can you take a look at it, please, and let me know if you've seen it before?

A. It's the Declaration of Dr. Baldwin. I have seen it before.

Q. And earlier today, Counsel for Emcure asked you whether or not you had reviewed additional documents since preparing your Declaration. Is this one of the additional documents that you did review?

A. Since preparing my Declaration I did review this one and the, the Exhibits attached to it.

Q. Now, I'd like to turn your attention to page 3 of Exhibit No. 2, and

S. G. DAVIES

in particular looking at the section II, which is entitled "A Person of Ordinary Skill in the Art." Do you see that?

A. I see that, yes.

Q. Did you review this section of Dr. Baldwin's report?

A. I did, yes.

Q. And when you reviewed this section of Dr. Baldwin's report did you agree with everything that Dr. Baldwin said?

MR. HU: Objection. This is way beyond the scope of anything we asked him on direct.

MR. GUERRIERO: I also object to the form.

MS. HARDMAN: And for clarity, Teva joins in objections made by other Counsel, Counsel for other parties.

A. Can you repeat the question, please?

Q. Sure. When you reviewed Dr. Baldwin's report, and in particular

reviewing section II entitled "A Person of Ordinary Skill in the Art," did you agree with everything that Dr. Baldwin said in this section?

A. I did not agree with what Dr. Baldwin has written in section II. I've written my own, my report, Declaration. I've listed my own view of a person with ordinary skill in the art. This coming from my experience of teaching such people and interacting with such people of over more than 40 years. In fact, I didn't understand parts of Dr. Baldwin's section II at all.

Q. Would you please explain your disagreement with section II and what you didn't understand about Dr. Baldwin's section II?

MR. HU: Objection. It's way beyond the scope of direct. Also, object to the form of the question.

A. In particular, in paragraph 9 for example, I don't understand why -- what he's trying to say when he says that his --

"A person of ordinary skill in the art in the context of the 372 patent, is a scientist involved in the research and development of new drugs who has a Ph.D. and/or medical degree and several years of experience in the field, with an amount of postgraduate experience depending on the level of formal education and particular experience in the field."

Because that seems -- I don't understand what the last part of that means at all. It's almost as though he's missed out a section in there that says with a bachelor degree and with an amount of postgraduate experience, depending on the level, which would then make it equivalent to the definition I put forth. I don't understand it as it's written. What he's trying to say.

Q. Now, turning your attention to section III of Dr. Baldwin's report entitled "Stereochemistry"? Did you review this section of his report?

A. I did.

MR. HU: Objection. It's way beyond the scope of direct. Seems to me you want to try to put in another Declaration, you can do it, but this is not the forum to use the deposition where your, your redirect is limited to the subjects brought up on cross, and I think it's totally inappropriate, and also object to the form of the question.

MS. HARDMAN: What I meant by my earlier statement is that I'm joining in all objections made by Counsel for other Defendants.

MR. RATLIFF: Thank you.

Q. Dr. Davies, would you please let me know if when you reviewed section III entitled "Stereochemistry" of Dr. Baldwin's report if you had any disagreements with what he said in this section?

MR. HU: I have the same objection. This whole line of questioning is totally out of bounds.

A. I set out in my report what I think a person with ordinary skill would understand, and that is very different to what Professor Baldwin has put in his report, and, so, yes, I do disagree with a lot of the things he writes.

Q. Do you believe his description of stereochemistry in paragraphs 10 through 26 is helpful to the court in understanding the proper interpretation of Claim 14 of the 372 patent?

MR. HU: Objection to the form of the question. Object. It's beyond the scope of the direct and seeks speculation as to what the judge is going to think.

A. I believe what I've said in my report is clearer than this. I think this goes into, into aspects that are not going to be helpful to the court to understand the construction of Claim 14.

Q. Turning your attention to paragraphs 27 of Dr. Baldwin's report, do you believe what he said here in paragraph

27 is helpful to the court?

MR. HU: Objection.

Q. In understanding the proper construction of Claim 14 of the 372 patent?

MR. HU: Same objections. I'm not going to say them again. To save time here.

A. I believe these could be misleading. The statements I put in my report I think are very clear on how to construe Claim 14.

Q. Turning your attention to paragraph 28 of Dr. Baldwin's report, did you review each of the documents that Dr. Baldwin sites in paragraph 28 of his report?

A. I read them all.

Q. And do you have any disagreements with the documents that he excited -- cited, or do you believe that they would be helpful to the court in determining the proper construction of Claim 14?

MR. HU: Same objection.

MS. HARDMAN: And objection, compound.

A. I don't believe these documents will be helpful to the court in deterring -- determining how to construe Claim 14.

Q. Would you please explain why?

MR. HU: Objection. This is not the forum to go beyond the scope and have him do a rebuttal when he wasn't asked about this.

I don't know if I need to do this here, but we're going to move to strike this whole line of exam, examination.

MR. RATLIFF: That's, that's fine. You can write your brief. You don't have to interrupt the deposition. I understand --

MR. HU: It's an objection.

MR. RATLIFF: Right. Just make your objection.

MR. HU: I did --

MR. RATLIFF: Just state it

simply and concisely. And you're not doing that, you're not doing that --

MR. HU: I just did.

MR. RATLIFF: Okay. So continue simply and concisely.

A. I think that Dr. Baldwin is mischaracterizing the way in which these documents use structures, and so that's not helpful to the court.

Q. Please explain how in your view he's mischaracterizing these documents that he's cited in paragraph 28 of his Declaration?

MR. HU: Same objection: Beyond the scope of the direct and form of the question, and it seeks speculation as to what the judge is going to think.

A. Well, some of these documents use structural drawings to depict single enantiomers and racemates alike, and the implication here is that they depict just racemates.

Q. So do you disagree with the

implication made by Dr. Baldwin with respect to paragraph 28 of his Declaration?

MR. HU: Same objection.

A. I disagree. Chemical structure is used by, commonly by a chemist to depict both single enantiomers, racemates, and any mixture in between, not just racemates.

Q. Drawing your attention to page 29 of Dr. Baldwin's Declaration. Did you read this paragraph?

A. I did read this --

MR. HU: Same objection. I'm sorry. Same objection.

Q. Did you also read Exhibit 14 that's cited to within paragraph 29?

A. I did read that, yes.

Q. Do you believe --

MR. RATLIFF: Strike that.

Q. Do you have any disagreements with what Dr. Baldwin said with respect to paragraph 29 of his Declaration?

MR. HU: Same objection.

A. I think he's mischaracterizing the way that the inventors are using the

structures drawn in Exhibit 14. And again, it's common practice for a chemist to use a single structure to depict either an enantiomer or the racemate, or any picture in between, not just the racemate.

Q. Turning your attention to Section IV of Dr. Baldwin's Declaration entitled "The 372 Patent." Let me know when you have that, sir.

A. I have that.

Q. Did you review this section of Dr. Baldwin's Declaration?

MR. HU: Objection. It's beyond the scope of direct. Totally inappropriate.

A. I did review this section, yes.

Q. When you reviewed it did you agree with everything that Dr. Baldwin said in this section?

A. I do not agree with many of the things that Dr. Baldwin says in this section. I don't believe that this analysis is how a POSA would do the analysis to construe Claim 14.

this portion of Dr. Baldwin's Declaration?

A. I did read section V.

Q. Do you believe that section V would be helpful to the court in understanding the proper interpretation of Claim 14 of the 372 patent?

A. I do not think it would be helpful because it's not put in the context of the 372 patent.

MR. HU: I'm sorry. I object to that, obviously.

MR. RATLIFF: Well, lead.

MR. HU: Yeah, maybe. There are enough of them before that. I think the point is made.

MR. RATLIFF: You have to object to each question. That's how it works.

MR. HU: Thank you for the lesson --

MR. RATLIFF: If you have a proper objection.

Q. Dr. Davies, if we have a Markman Hearing in this case and the judge

Q. Would you please explain in more detail why you believe that the analysis that Dr. Baldwin set forth in section IV of his Declaration is not how a POSA would do the analysis in terms of understanding Claim 14 of the 372 patent?

MR. HU: Same objection.

A. Well, a POSA would look at Claim 14 and see the structure there. I mean read the specification of the patent. And in the specification of the patent, in Example 1-(a) through (e), it is very clear that that Claim 14 is referring to Lurasidone. Lurasidone's an enantiomer, racemate, and any mixture in between, and that is not the analysis that Professor Baldwin has done.

Q. Turning your attention to section V of Dr. Baldwin's Declaration entitled "Acid Addition Salts." Let me know when you have that, sir.

MR. HU: Same objection.

A. I have it.

Q. Did you read -- did you read

asked you whether or not you have disagreements with Dr. Baldwin's opinions as set forth in his report, would you be happy to explain to the judge your disagreements with Dr. Baldwin's opinions?

MR. HU: Objection. Same objection.

A. I would be very happy to explain to the court, and my disagreements with Dr. Baldwin, and I would explain to the court how I think a person with ordinary skill in the art would actually construe Claim 14.

Q. And, Doctor, if any of the Defendants represented here, either Emcure, InvaGen, or Teva have any questions whatsoever regarding your disagreements with Dr. Baldwin's Declaration would you be happy to try to answer their questions here today?

A. Of course.

MR. RATLIFF: I have no further questions for you, sir, at this time.

FURTHER EXAMINATION BY

EXHIBIT 12

United States Patent [19]
Roth

[11] **Patent Number: 4,681,893**
[45] **Date of Patent: Jul. 21, 1987**

[54] **TRANS-6-[2-(3- OR 4-CARBOXAMIDO-SUBSTITUTED PYRROL-1-YL)ALKYL]-4-HYDROXYPYRAN-2-ONE INHIBITORS OF CHOLESTEROL SYNTHESIS**

[75] Inventor: **Bruce D. Roth**, Ann Arbor, Mich.

[73] Assignee: **Warner-Lambert Company**, Morris Plains, N.J.

[21] Appl. No.: **868,867**

[22] Filed: **May 30, 1986**

[51] **Int. Cl.**[4] **A61K 31/40**; A61K 31/35; C07D 207/327

[52] **U.S. Cl.** **514/422**; 514/423; 546/256; 546/275; 548/517; 548/537

[58] **Field of Search** 548/517, 537; 514/422, 514/423

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,983,140	9/1976	Endo et al.	549/292
4,049,495	9/1977	Endo et al.	435/125
4,137,322	1/1979	Endo et al.	548/344 X
4,198,425	4/1980	Mitsui et al.	514/460
4,255,444	3/1981	Oka et al.	549/292 X
4,262,013	4/1981	Mitsui et al.	549/292 X
4,375,475	3/1983	Willard et al.	514/460

OTHER PUBLICATIONS

Singer, et al.; Proc. Soc. Exper. Biol. Med.; vol. 102, pp. 370–373, (1959).
Hulcher; Arch. Biochem. Biophys., vol. 146, pp. 422–427, (1971).
Brown, et al.; New England Jour. of Med., vol. 305, No. 9, pp. 515–517, (1981).
Brown, et al.; J. Chem. Soc. Perkin I, (1976), pp. 1165–1170.
Journal of the Americas Medical Assoc.; (1984), vol. 251, pp. 351–364, 365–374.

Primary Examiner—Joseph Paul Brust
Attorney, Agent, or Firm—Jerry F. Janssen

[57] **ABSTRACT**

Certain trans-6-[2-(3- or 4-carboxamido-substituted pyrrol-1-yl)alkyl]-4-hydroxypyran-2-ones and the corresponding ring-opened acids derived therefrom which are potent inhibitors of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG CoA reductase and are thus useful hypolipidemic or hypocholesterolemic agents. Pharmaceutical compositions containing such compounds, and a method of inhibiting the biosynthesis of cholesterol employing such pharmaceutical compositions are also disclosed.

9 Claims, No Drawings

TRANS-6-[2-(3- OR 4-CARBOXAMIDO-SUBSTITUTED PYRROL-1-YL)ALKYL]-4-HYDROXYPYRAN-2-ONE INHIBITORS OF CHOLESTEROL SYNTHESIS

BACKGROUND OF THE INVENTION

The present invention is related to compounds and pharmaceutical compositions useful as hypocholesterolemic and hypolipidemic agents. More particularly, this invention concerns certain trans-6-[2-(3- or 4-carboxamidosubstitutedpyrrol-1-yl)alkyl]-4-hydroxypyran-2-ones and the corresponding ring-opened acids derived therefrom which are potent inhibitors of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG CoA reductase), pharmaceutical compositions containing such compounds, and a method of inhibiting the biosynthesis of cholesterol employing such pharmaceutical compositions.

High levels of blood cholesterol and blood lipids are conditions involved in the onset of arteriosclerosis. It is well known that inhibitors of HMG-CoA reductase are effective in lowering the level of blood plasma cholesterol, especially low density lipoprotein cholesterol (LDL-C), in man (cf. M. S. Brown and J. L. Goldstein, *New England Journal of Medicine*, 305, No. 9, 515–517 (1981). It has now been established that lowering LDL-C levels affords protection from coronary heart disease (cf. *Journal of the American Medical Association*, 251, No. 3, 351–374 (1984).

Moreover, it is known that certain derivatives of mevalonic acid (3,5-dihydroxy-3-methylpentanoic acid) and the corresponding ring-closed lactone form, mevalonolactone, inhibit the biosynthesis of cholesterol (cf. F. M. Singer et al., *Proc. Soc. Exper. Biol. Med.*, 102: 370 (1959) and F. H. Hulcher, *Arch. Biochem. Biophys.*, 146: 422 (1971)).

U.S. Pat. Nos. 3,983,140; 4,049,495 and 4,137,322 disclose the fermentative production of a natural product, now called compactin, having an inhibitory effect on cholesterol biosynthesis. Compactin has been shown to have a complex structure which includes a mevalonolactone moiety (Brown et al., *J. Chem. Soc. Perkin* I (1976) 1165.

U.S. Pat. No. 4,255,444 to Oka et al. discloses several synthetic derivatives of mevalonolactone having antilipidemic activity.

U.S. Pat. Nos. 4,198,425 and 4,262,013 to Mitsue et al. disclose aralkyl derivatives of mevalonolactone which are useful in the treatment of hyperlipidemia.

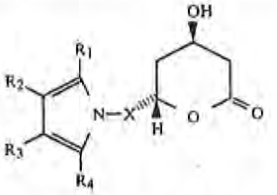
U.S. Pat. no. 4,375,475 to Willard et al. discloses certain substituted 4-hydroxytetrahydropyran-2-ones which, in the 4(R)-trans-stereoisomeric form, are inhibitors of cholesterol biosynthesis.

Published PCT application No. WO 84/01231 discloses certain indole analogs and derivatives of mevalonolactone having utility as hypolipoproteinemic and antiatherosclerotic agents.

SUMMARY OF THE INVENTION

In accordance with the present invention, there are provided certain trans-6-[2-(3- or 4-carboxamido-substituted pyrrol-1-yl)alkyl]-4-hydroxypyran-2-ones and the corresponding ring-opened hydroxy-acids derived therefrom which are potent inhibitors of cholesterol biosynthesis by virtue of their ability to inhibit the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase).

In particular, in its broadest aspect the present invention provides compounds of structural formula I



I

wherein X is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ or $-CH_2CH(CH_3)-$.

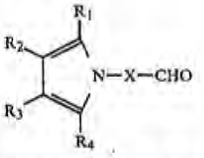
R_1 is 1-naphthyl; 2-naphthyl; cyclohexyl; norbornenyl; 2-, 3-, or 4-pyridinyl; phenyl, phenyl substituted with fluorine, chlorine, bromine, hydroxyl; trifluoromethyl; alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms.

Either R_2 or R_3 is $-CONR_5R_6$ where R_5 and R_6 are independently hydrogen; alkyl of from one to six carbon atoms; 2-, 3-, or 4-pyridinyl; phenyl; phenyl substituted with fluorine, chlorine, bromine, cyano, trifluoromethyl, or carboalkoxy of from three to eight carbon atoms; and the other of R_2 or R_3 is hydrogen; alkyl of from one to six carbon atoms; cyclopropyl; cyclobutyl; cyclopentyl; cyclohexyl; phenyl; or phenyl substituted with fluorine, chlorine, bromine, hydroxyl; trifluoromethyl; alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms.

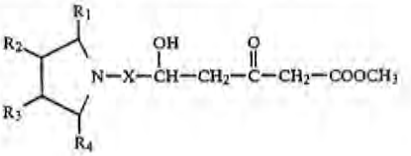
R_4 is alkyl of from one to six carbon atoms; cyclopropyl; cyclobutyl; cyclopentyl; cyclohexyl; or trifluoromethyl.

Also contemplated as falling within the scope of the present invention are the hydroxy acids, and pharmaceutically acceptable salts thereof, derived from the opening of the lactone ring of the compounds of structural formula I above.

In another aspect of the present invention, there is provided a method of preparing the compounds of structural formula I above which comprises the steps of (a) first reacting a substituted [(pyrrol-1-yl)alkyl]aldehyde compound of the formula

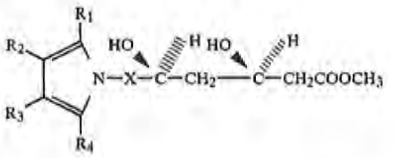


with the dilithio or sodio-lithio salt of methyl acetoacetate to form a compound of the structure



(b) reducing the product of step (a) with a trialkylborane compound such as tributylborane in the presence of sodium borohydride in an inert solvent;

(c) oxidizing the product of step (b) with alkaline aqueous hydrogen peroxide solution to produce a compound of the formula



and

(d) cyclizing the product step (c) to a lactone of formula I above by heating in an inert solvent such as toluene or, alternatively converting the product of step (c) to a pharmaceutically acceptable salt by conventional methods.

In yet another aspect, the present invention provides pharmaceutical compositions useful as hypolipidemic or hypocholesterolemic agents comprising a hypolipidemic or hypocholesterolemic effective amount of a compound in accordance with this invention as set forth above, in combination with a pharmaceutically acceptable carrier.

In another aspect, the present invention provides a method of inhibiting cholesterol biosynthesis in a patient in need of such treatment by administering an effective amount of a pharmaceutical composition as defined above.

DETAILED DESCRIPTION

The compounds of the present invention comprise a class of trans-6-[2-(3- or 4-carboxamidosubstituted pyrrol-1-yl)alkyl]-4-hydroxypyran-2-ones in which the pyran-2-one moiety is attached, through an alkyl chain, to the substituted pyrrole nucleus at the nitrogen, or 1-position, of the pyrrole. The alkyl group may be methylene, ethylene, propylene, or methylethylene. The preferred alkyl chain linking the substituted pyrrole nucleus and the 4-hydroxypyran-2-one ring is ethylene.

The compounds of structural formula I above possess two asymmetric carbon centers, one at the 4-hydroxy position of the pyran-2-one ring, and the other at the 6-position of the pyran-2-one ring where the alkylpyrrole group is attached. This asymmetry gives rise to four possible isomers, two of which are the R-cis- and S-cis-isomers and the other two of which are the R-trans- and S-trans-isomers. This invention contemplates only the trans- form of the compounds of formula I above.

In the compounds of the present invention, position 2 of the substituted pyrrole nucleus is substituted with 1-naphthyl; 2-naphthyl; cyclohexyl; norbornenyl; 2-, 3-, or 4-pyridinyl; phenyl, phenyl substituted with fluorine, chlorine, bromine, hydroxyl; trifluoromethyl; alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms. Preferred substituent groups at the 2-position of the pyrrole nucleus are phenyl and substituted phenyl.

In the compounds of this invention, position 5 of the pyrrole nucleus is substituted with alkyl of from one to six carbon atoms; cyclopropyl; cyclobutyl; cyclopentyl; cyclohexyl; or trifluoromethyl. Preferred substituents are alkyl or trifluoromethyl with isopropyl being particularly preferred.

The preferred reaction sequence which is used to prepare compounds of the present invention involves the cycloaddition of a disubstituted acetylene, in which one substituent is carboxamido or N-substituted carboxamido, to an appropriately substituted N-acylaminocarboxylic acid to form a substituted pyrrole. This addition may occur in either of two ways, leading to a substituted pyrrole addition product in which the carboxamido substituent resides on either carbon 3 or 4 of the pyrrole nucleus.

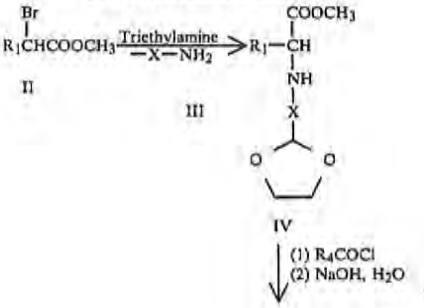
Thus, in compounds of the present invention, the substituent at either position 3 or 4 of the pyrrole nucleus is $-CONR_5R_6$ where R_5 and R_6 are independently hydrogen; alkyl of from one to six carbon atoms; 2-, 3-, or 4-pyridinyl; phenyl; phenyl substituted with fluorine, chlorine, bromine, cyano, trifluoromethyl, or carboalkoxy of from three to eight carbon atoms and the other of the two positions is unsubstituted or is substituted with alkyl of from one to six carbon atoms; cyclopropyl; cyclobutyl; cyclopentyl; cyclohexyl; phenyl; or phenyl substituted with fluorine, chlorine, bromine, hydroxyl; trifluoromethyl; alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms.

Preferred groups for R_5 and R_6 are hydrogen, phenyl, or substituted phenyl. In a particularly preferred group of compounds within the present invention, R_5 is hydrogen and R_6 is phenyl or substituted phenyl.

The compounds of this invention are prepared by the general reaction scheme outlined in Reaction Sequence 1 which takes advantage of the chemistry of mesionic compounds of the type described originally by R. Huisgen et al., *Ang. Chem. Int. Ed.*, 3: 136 (1964).

The known, or readily prepared, α-haloesters of structural formula II are reacted with the known 2-[1-(2-aminoalkyl)]-1,3-dioxalane, III, in the presence of an acid scavenger such as triethylamine to produce the N-alkyl-α-aminoesters, IV. The aminoesters, IV are

REACTION SEQUENCE 1



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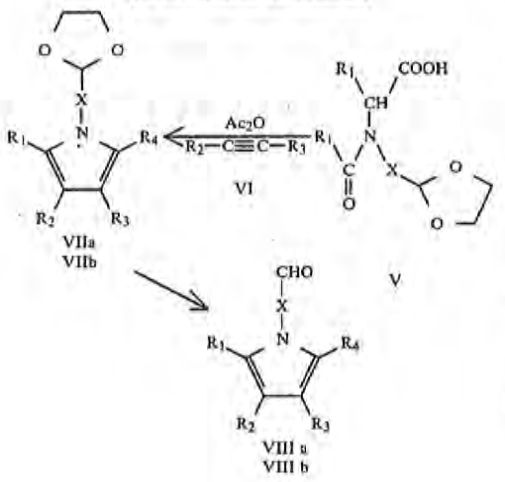
REACTION SEQUENCE 1



VIIa
VIIb

VI

V

VIII a
VIII b

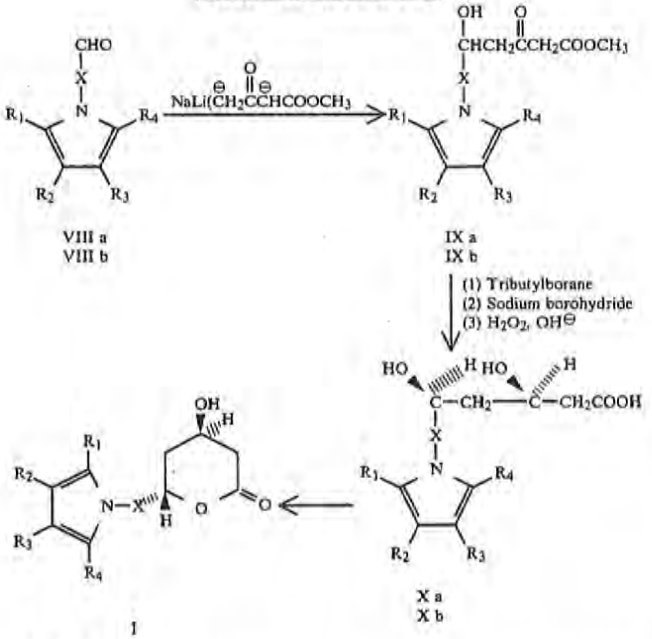
known in the art, and subsequently further purified, if desired, by recrystallization. On the other hand, in the case where R_4 is 1-methylethyl, the cyclo-addition reaction yields predominantly one product which can be purified by recrystallization alone.

Hydrolysis of the acetal function of compounds VIIa and VIIb in aqueous acid solution affords the aldehydes VIIIa and VIIIb. The aldehydes, VIII, are further converted to compounds of the present invention by the processes depicted in Reaction Sequence 2.

The aldehyde compounds, VIII, are reacted with the dilithium or lithio-sodio salt of methyl acetoacetate to produce the corresponding 7-(substituted-pyrrolyl)-5-hydroxy-3-oxoheptanoates, IX. The heptanoates, IX, are dissolved in a polar solvent such as tetrahydrofuran, through which a small amount of air has been bubbled. A slight excess of a trialkylborane, such as tributylborane, is added to the mixture which is then cooled to a temperature of preferably between about 0° C. and −78° C. after which sodium borohydride is added.

The mixture is stirred for about one to two hours and then oxidized by the addition of basic aqueous hydrogen peroxide solution. The reaction produces the 7-(substituted-pyrrolyl)-3,5-dihydroxyheptanoic acids,

REACTION SEQUENCE II



VIII a
VIII b

IX a
IX b

X a
X b

acylated with an acid halide and subsequently hydrolyzed in aqueous base solution to produce the N-acyl-N-alkyl aminoacids, V.

The N-acyl-N-alkyl aminoacids, V, are reacted with the appropriately substituted carboxamido acetylenic compounds, VI, in the presence of an acid anhydride to produce a mixture of the isomeric substituted pyrrole compounds VIIa and VIIb. Depending upon the substituents present, this cyclo-addition reaction affords differing ratios of the two products. For example, in the situation where R_4 is trifluoromethyl, the reaction yields roughly equimolar amounts of the two isomeric products. In such situations, the two isomeric products are separated by chromatographic techniques well

X, in which the product contains a predominance of the desired R*,R* configuration at carbon atoms three and five which bear the hydroxy groups.

The acids may be converted to a corresponding pharmaceutically acceptable salt by conventional means, if desired, or cyclized to the trans-6-[2-(substituted-pyrrol-1-yl)alkyl]pyran-2-ones, I, by dehydration in an inert solvent such as refluxing toluene with azeotropic removal of water. This cyclization step has been found to produce material containing from 85–90% of the desired trans-configuration of the 4-hydroxy group relative to the 6-(substituted-pyrrol-1-yl)alkyl group on the pyran-2-one lactone ring.

The ring-opened hydroxy acids of structural formula II above are intermediates in the synthesis of the lactone compounds of formula I and may be used in their free acid form or in the form of a pharmaceutically acceptable metal or amine salt in the pharmaceutical method of the present invention. These acids react to form pharmaceutically acceptable metal and amine salts. The term "pharmaceutically acceptable metal salt" contemplates salts formed with the sodium, potassium, calcium, magnesium, aluminum, iron, and zinc ions. The term "pharmaceutically acceptable amine salt" contemplates salts with ammonia and organic nitrogenous bases strong enough to form salts with carboxylic acids. Bases useful for the formation of pharmaceutically acceptable nontoxic base addition salts of compounds of the present invention form a class whose limits are readily understood by those skilled in the art.

The free acid form of compounds of the present invention may be regenerated from the salt form, if desired, by contacting the salt with a dilute aqueous solution of an acid such as hydrochloric acid.

The base addition salts may differ from the free acid forms of the compounds of this invention in such physical characteristics as solubility and melting point, but are otherwise considered equivalent to the free acid form for the purposes of this invention.

The compounds of the present invention may exist in solvated or unsolvated form. In general, the solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like, are equivalent to the unsolvated forms for the purposes of this invention.

The compounds of this invention are useful as hypocholesterolemic or hypolipidemic agents by virtue of their ability to inhibit the biosynthesis of cholesterol through inhibition of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase).

The ability of compounds of the present invention to inhibit the biosynthesis of cholesterol was measured by two methods. A first method (designated CSI screen) utilized the procedure described by R. E. Dugan et al., *Archiv. Biochem. Biophys.*, (1972), 152, 21-27. In this method, the level of HMG-CoA enzyme activity in standard laboratory rats is increased by feeding the rats a chow diet containing 5% cholestyramine for four days, after which the rats are sacrificed.

The rat livers are homogenized, and the incorporation of cholesterol-^{14}C-acetate into nonsaponifiable lipid by the rat liver homogenate is measured. The micromolar concentration of compound required for 50% inhibition of sterol synthesis over a one-hour period is measured, and expressed as an IC_{50} value.

A second method (designated COR screen) employed the procedure detailed by T. Kita, et al., *J. Clin. Invest.*, (1980), 66: 1094–1100. In this method, the amount of ^{14}C-HMG-CoA converted to ^{14}C-mevalonate in the presence of a purified enzyme preparation of HMG-CoA reductase was measured. The micromolar concentration of compound required for 50% inhibition of cholesterol synthesis was measured and recorded as an IC_{50} value.

The activity of several representative examples of compounds in accordance with the present invention appears in Table 1, and is compared with that of the prior art compound, compactin.

For preparing pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersable granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be an encapsulating material.

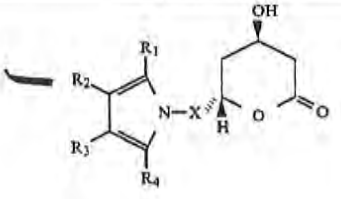
In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component. In tablets, the active compound is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

For preparing suppositories, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted, and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient sized molds and allowed to cool and solidify.

Powders and tablets preferably contain between about 5 to about 70% by weight of the active ingredient. Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is

TABLE 1



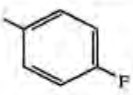
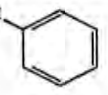
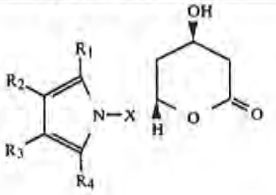
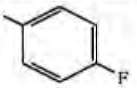
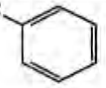
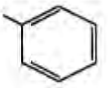
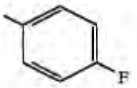
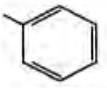
Compound	X	R_1	R_2	R_3	R_4	IC_{50} (Micromoles/liter) CSI	COR
1	$-CH_2CH_2-$			$-CONH-$ 	$-CH(CH_3)_2$	0.035	0.050

TABLE 1-continued



Compound	X	R_1	R_2	R_3	R_4	IC_{50} (Micromoles/liter) CSI	COR
2	$-CH_2CH_2-$		$-CONH-$ 		$-CF_3$	0.40	0.40
3	$-CH_2CH_2-$			$-CONH-$ 	$-CF_3$	0.018	0.020
Compactin (Prior art)						0.026	0.028

surrounded by a carrier, which is thus in association with it. In a similar manner, cachets are also included. Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

Liquid form preparations include solutions suitable for oral or parenteral administration, or suspensions and emulsions suitable for oral administration. Sterile water solutions of the active component or sterile solutions of the active component in solvents comprising water, ethanol, or propylene glycol may be mentioned as examples of liquid preparations suitable for parenteral administration.

Sterile solutions may be prepared by dissolving the active component in the desired solvent system, and then passing the resulting solution through a membrane filter to sterilize it or, alternatively, by dissolving the sterile compound in a previously sterilized solvent under sterile conditions.

Aqueous solutions for oral administration can be prepared by dissolving the active compound in water and adding suitable flavorants, coloring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural or synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is divided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparation, for example, packeted tablets, capsules, and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms.

In therapeutic use as hypolipidemic or hypocholesterolemic agents, the compounds utilized in the pharmaceutical method of this invention are administered to the patient at dosage levels of from 40 mg to 600 mg per day. For a normal human adult of approximately 70 kg or body weight, this translates to a dosage of from about 0.5 mg/kg to about 8.0 mg/kg of body weight per day.

The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of optimum dosages for a particular situation is within the skill of the art.

The following examples illustrate particular methods for preparing compounds in accordance with this invention. These examples are illustrative and are not to be read as limiting the scope of the invention as it is defined by the appended claims.

EXAMPLE 1

Preparation of trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo2H-pyran-2-yl)ethyl]-pyrrole-3-carboxamide

Step A: Preparation of α-[[2-(1,3-dioxalan-2-yl)ethyl]amino]-4-fluorobenzeneacetic acid, ethyl ester

A solution of 26 g (220 mmol) of 2-[1-(2-aminoethyl)]-1,3-dioxalane in 50 ml of acetonitrile was added at room temperature with stirring to a solution of 200 mmol of α-bromo-4-fluorobenzeneacetic acid, ethyl ester (J. W. Epstein et al., *J. Med. Chem.*, 24: 481–490 (1981)) and 42 ml (300 mmol) of triethylamine in 350 ml of acetonitrile. The resulting mixture was stirred at room temperature overnight and then poured into 500 ml of diethyl ether. The resulting suspension was extracted with 300 ml of water and then twice with 300-ml portions of 2M hydrochloric acid. The combined extracts were made basic with 25% aqueous sodium hydroxide solution and extracted twice with 500-ml portions of ethyl acetate. The ethyl acetate extracts were combined, washed successively with water and brine, and then dried over anhydrous magnesium sulfate. The drying agent was removed by filtration, and the residue concentrated to yield 49.5 g of α-[[2-(1,3-dioxalan-2-yl)ethyl]amino]-4-fluorobenzeneacetic acid, ethyl ester.

The 90 MHz proton magnetic resonance spectrum of the product in deuterochloroform exhibited signals at 1.18 (triplet, 3H, J=7 Hz); 1.85 (multiplet, 2H); 2.20

(broad singlet, 1H); 2.6 (multiplet, 2H); 3.85 (multiplet, 4H); 4.1 (quartet, 2H, J=7 Hz); 4.22 (singlet, 1H); 4.83 (triplet, 1H, J=4.5 Hz); and 6.8–7.3 (multiplet, 4H) parts per million downfield from tetramethylsilane.

Step B. Preparation of α-[[2-(1,3-dioxolan-2-yl)ethyl]-(2-methyl-1-oxopropyl)amino]-4-fluorobenzeneacetic acid, ethyl ester.

Thirty grams (100 mmol) of α-[[2-(1,3-dioxalan-2-yl)ethyl]amino]-4-fluorobenzeneacetic acid, ethyl ester from Step A were dissolved in 200 ml of dichloromethane together with 28.6 ml (205 mmol) of triethylamine and the resulting mixture was cooled to 0° C. under dry nitrogen. A solution of 11 ml (105 mmol) of isobutyryl chloride in 50 ml of dichloromethane was slowly added with stirring. After addition was complete, the mixture was stirred for an additional 60 minutes and then poured into 100 ml of diethyl ether. The ether solution was washed successively with portions of water, 2M hydrochloric acid, sodium bicarbonate solution, and brine, and then dried over anhydrous magnesium sulfate. Evaporation of the solvents yielded 35 g of α-[[2-(1,3-dioxolan-2-yl)-ethyl]-(2-methyl-1-oxopropyl)amino]-4-fluorobenzene-acetic acid, ethyl ester.

The 90 MHz proton magnetic resonance spectrum of a deuterochloroform solution of the product exhibited signals at 1.2 (multiplet, 9H); 1.7 (multiplet, 2H); 2.85 (multiplet, 1H); 3.35 (multiplet, 2H); 3.80 (multiplet, 4H); 4.20 (quartet, 2H, J=7 Hz); 4.60 (triplet, 1H, J=4.5 Hz); 5.81 (singlet, 1H); and 6.8–7.3 (multiplet, 4H) parts per million downfield from tetramethylsilane.

Step C. Preparation of α-[[2-(1,3-dioxolan-2-yl)ethyl]-(2-methyl-1-oxopropyl)amino]-4-fluorobenzeneacetic acid

A solution of 35 g (95.3 mmol) of the ester from Step B and 12 g (300 mmol) of sodium hydroxide in 480 ml of 5:1 methanol water was heated under reflux and stirred for two hours. The solution was cooled to room temperature, concentrated, and diluted by the addition of 500 ml of water. The resulting solution was extracted with ether and the aqueous layer was acidified with ice-cold 6M hydrochloric acid and then extracted twice with 300-ml portions of ethyl acetate.

The combined extracts were washed with brine, dried over anhydrous magnesium sulfate, and evaporated to yield 30 g of crude α-[[2-(1,3-dioxolan-2-yl)ethyl]-(2-methyl-1-oxopropyl)amino]-4-fluorobenzeneacetic acid which was used without further purification.

The 90 MHz proton magnetic resonance spectrum of a deuterochloroform solution of the product exhibited signals at 1.11 (doublet, 6H, J=7 Hz); 1.4–1.9 (multiplet, 2H); 2.85 (multiplet, 1H); 3.32 (multiplet, 2H); 3.75 (multiplet, 4H); 4.52 (triplet, 1H, J=4.5 Hz); 5.73 (singlet, 1H); and 6.8–7.3 (multiplet, 4H) parts per million downfield from tetramethylsilane.

Step D. Preparation of N,3-diphenylpropynamide

A solution of 171 mmol of dicyclohexylcarbodiimide in 250 ml of dichloromethane was added dropwise over a two hour period at 0° C. to a suspension of 171 mmol of propiolic acid, 179.6 mmol of aniline, and 5 mmol of 4-dimethylaminopyridine in 400 ml of dichloromethane. After addition was complete, the mixture was stirred for an additional 30 minutes and then diluted with diethyl ether. The resulting mixture was filtered through silica gel, concentrated, and the residue recrystallized to provide 30.5 g of N,3-diphenyl-2-propynamide, mp 122°–123° C.

Analyzed for $C_{15}H_{13}NO$: Calc.: C, 80.69%; H, 5.87%; N, 6.27%; Found: C, 80.54%; H, 5.58%; N, 6.52%.

The infrared spectrum of a KBr pellet of the compound showed principal peaks at 2215, 1630, 1595,1549, 1490, 1445, 1330, 756, and 691 reciprocal centimeters.

Step E. Preparation of 1-[2-(1,3-dioxalan-2-yl)ethyl]-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1H-pyrrole-3-carboxamide

A solution of 95 g (280 mmol) of α-[[2-(1,3-dioxolan-2-yl)ethyl]-(2-methyl-1-oxopropyl)amino]-4-fluorobenzeneacetic acid, prepared as described in Step C above, and 98 g (439 mmol) of N,2-diphenylpropenoic carboxamide, prepared as described in Step D above, was heated at 90° C. with stirring for four hours, (Vigorous gas evolution occurred for two hours.) After this time, the mixture was cooled to room temperature and chromatographed twice on silica gel, eluting with 4:1 hexane:ethyl acetate to separate the product (R_f=0.35) from the starting material (R_f=0.5).

Recrystallization of the product from isopropyl ether provided 59.5 g (119.3 mmol) of 1-[2-(1,3-dioxalan-2-yl)ethyl]-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1H-pyrrole-3-carboxamide, mp 159°–162° C.

Analyzed for $C_{31}H_{31}FN_2O_3$: Calc.: C, 74.68%; H, 6.27%; N, 5.62%; Found: C, 75.04%; H, 6.12%; N, 5.89%.

Step F. Preparation of 5-(4-fluorophenyl)-2-(1-methylethyl)-1-(3-oxopropyl)-N,4-diphenyl-1H-pyrrole-3-carboxamide

A solution of 59 g (118.3 mmol) of 1-[2-(1,3-dioxalan-2-yl)ethyl]-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1H-pyrrole-3-carboxamide, from Step E above, and 0.4 ml of concentrated hydrochloric acid in 1200 ml of anhydrous ethanol was heated under reflux with stirring for 24 hours. After this time the mixture was cooled to room temperature, concentrated, and the residue taken up in 1200 ml of 3:1 acetone:water and 5 g of p-toluenesulfonic acid was added. This mixture was heated under reflux with stirring for two days after which time the solution was cooled to room temperature and partitioned between 1 liter of diethyl ether and 200 ml of brine solution.

The organic phase was separated, washed successively with sodium bicarbonate solution and brine, dried over anhydrous magnesium sulfate and concentrated. The oil which resulted was dissolved in the minimum amount required of hot isopropyl ether. The crystals which formed upon cooling were collected by filtration to yiled 36.8 g of 5-(4-fluorophenyl)-2-(1-methylethyl)-1-(3-oxopropyl)-N,4-diphenyl-1H-pyrrole-3-carboxamide. A further crop of 9.8 g of crystals were obtained from the mother liquor.

Analyzed for $C_{29}H_{27}FN_2O_3$: Calc.: C, 76.63%; H, 5.99%; N, 6.16%; Found: C, 76.48%; H, 6.20%; N, 6.14%.

Step G. Preparation of 2-(4-fluorophenyl)-δ-hydroxy-5-(1-methylethyl)-β-oxo-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, methyl ester

A solution of methyl acetoacetate (26.4 ml, 243 mmol) in 250 ml of anhydrous tetrahydrofuran was added dropwise to a stirred suspension of hexane-washed sodium hydride (6.4 g, 267 mmol) in 200 ml of tetrahydrofuran at 0° C. When gas evolution was complete, 97.2 ml of 2.5M n-butyl lithium was added dropwise over a period of 60 minutes.

The resulting solution was stirred for 30 minutes at 0° C. and then cooled to −78° C. after which a solution of

36.8 g (80.9 mmol) of 5-(4-fluorophenyl)-2-(1-methylethyl)-1-(3-oxopropyl)-N,4-diphenyl-1H-pyrrole-3-carboxamide, from Step F above, in 100 ml of tetrahydrofuran was added over a period of thirty minutes. The resulting solution was stirred for 30 minutes at −78° C. and then warmed to 0° C. where it was held for an additional 60 minutes.

The mixture was then acidified by the dropwise addition of 300 ml of ice-cold 3M hydrochloric acid, diluted with ether, washed successively with water and brine, dried over anhydrous magnesium sulfate, and concentrated. Flash chromatography of the residue yielded 37.9 g of 2-(4-fluorophenyl)-δ-hydroxy-5-(1-methylethyl)-β-oxo-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, methyl ester.

The 90 MHz proton magnetic resonance spectrum of the product exhibited signals at 1.50 (doublet, 6H, J=7 Hz); 1.8 (multiplet, 2H); 2.45 (doublet, 2H, J=7 Hz); 2.8 (broad, 1H); 3.33 (singlet, 2H); 3.5 (multiplet, 1H); 3.67 (singlet, 3H); 3.8–4.0 (multiplet, 2H); and 6.8–7.3 (multiplet, 14H) parts per million downfield from tetramethylsilane.

Step H. Preparation of R*,R*-2-(4-fluorophenyl-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid and trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide

Air (60 ml) was bubbled via a syringe through a solution of 2-(4-fluorophenyl)-δ-hydroxy-5-(1-methylethyl)-β-oxo-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, methyl ester (48 g, 84.1 mmol) and 92.5 ml of 1M tributylborane in 100 ml of anhydrous tetrahydrofuran. The mixture was stirred overnight at room temperature and then cooled to −78° C. Sodium borohydride (3.85 g, 101.8 mmol) was added to the cooled mixture in one portion. The mixture was allowed to warm slowly to 0° C. over a period of three hours, during which there was vigorous gas evolution.

The dry ice-acetone bath applied to the reaction vessel was replaced by an ice bath and 18.3 ml of glacial acetic acid were added dropwise, followed by 204 ml of 3M aqueous sodium hydroxide solution and 30.5 ml of 30% aqueous hydrogen peroxide solution.

The mixture was vigorously stirred while being allowed to warm to room temperature overnight. The mixture was then partitioned between diethyl ether and water and the aqueous layer was separated, acidified, and extracted with ethyl acetate.

The ethyl acetate extract was washed with brine, dried, and evaporated to yield crude R*,R*-2-(4-fluorophenyl-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid which was used without further purification.

The crude acid was taken up in toluene and lactonized by heating under reflux for six hours. This mixture was chromatographed to provide 30 g of trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide as a foamy solid, mp 90°–97° C.

Analyzed for $C_{33}H_{33}FN_2O_4$: Calc.: C, 73.31%; H, 6.15%; N, 5.18%; Found: C, 73.46%; H, 6.31%; N, 5.28%.

This material was found by HPLC analysis to comprise a 9:1 molar ratio of the cis- and trans-isomeric forms of the product. Recrystallization from toluene-ethyl acetate yield the essentially pure trans-form, mp 148°–149° C.

EXAMPLE 2

Preparation of R*,R*-2-(4-fluoro-phenyl-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, sodium salt

A mixture of trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide (10 g, 18.5 mmol) and 0.74 g (18.5 mmol) of sodium hydroxide in 90 ml of a 1:2 mixture of tetrahydrofuran-water was cooled to 0° C. This mixture was allowed to warm slowly to 25° C., after which time it was concentrated and the residual solid dried under vacuum.

The infrared spectrum of the product exhibited principal absorption peaks at 3400, 1651, 1598, 1565, 1511, 1438, 1412, 1316, 1224, 1159, 844, 754, and 702 reciprocal centimeters.

The 90 MHz proton magnetic resonance spectrum of a hexadeutero dimethylsulfoxide solution of the product exhibited signals at 1.34 (doublet, J=7 Hz, 6H); 1.5 (multiplet, 4H); 1.80 (doublet of doublets, J=15, 8 Hz, 1H); 1.99 (doublet of doublets, J=15, 4 Hz, 1H); 3–4 (multiplet, 8H); 6.9–7.3 (multiplet, 12H); 7.50 (doublet, J=8 Hz, 2H); and 9.85 (singlet, 1H) parts per million downfield from tetramethylsilane.

EXAMPLES 3 AND 4

Preparation of trans-2-(4-fluorophenyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-5-(trifluoromethyl)-pyrrole-3-carboxamide and trans-5-(4-fluorophenyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-2-(trifluoromethyl)pyrrole-3-carboxamide

Step A. Preparation of α-[[2-(1,3-dioxalan-2-yl)ethyl]amino]-4-fluorobenzeneacetic acid.

α-[[2-(1,3-Dioxolan-2-yl)ethyl]amino]-4-fluorobenzeneacetic acid, ethyl ester (36.5 g, 122.8 mmol, prepared as described above in Example 1, Step A) was dissolved in 1500 ml of a 5:1 mixture of methanol-water together with 7.6 g of sodium hydroxide. This mixture was heated under reflux for a period of two and one-half hours after which time the solvents were removed under vacuum.

The solid residue was taken up in 325 ml of water and a mixture of 14 ml of glacial acetic in 28 ml of water was added with stirring. After stirring for a time, an additional 3 ml of glacial acetic acid were added and the mixture was chilled for 75 minutes. The solids were collected by filtration, washed with water and then ethyl acetate and dried to yield α-[[2-(1,3-dioxalan-2-yl)ethyl]amino]-4-fluorobenzeneacetic acid, mp 218°–220° C.

Step B. Preparation of a mixture of 5-(4-fluorophenyl)-1-(3-oxopropyl)-N,4-diphenyl-2-(trifluoromethyl)-1H-pyrrole-3-carboxamide and 2-(4-fluorophenyl)-1-(3-oxopropyl)-N,4-diphenyl-5-(trifluoromethyl)-1H-pyrrole-3-carboxamide

α-[[2-(1,3-Dioxalan-2-yl)ethyl]amino]-4-fluorobenzeneacetic acid (6.06 g, 22.5 mmol) was dissolved in 45 ml of trifluoroacetic anhydride and 7.47 g (33.8 mmol) of N,3-diphenyl-2-propynamide (prepared as described above in Example 1, Step D) was added. The resulting mixture was heated under reflux for a period of five and one-half hours. The mixture was then cooled, and 1.74

ml of trifluoroacetic acid were added and the mixture was stirred overnight.

The excess trifluoroacetic anhydride was removed under vacuum, and water was added, followed by sufficient acetone to give a homogenous solution. This solution was stirred at room temperature for three hours. The mixture was seeded with N,3-diphenyl-2-propynamide, and a precipitate formed. After three hours, this precipitate was removed by filtration.

The acetone was removed from the filtrate under vacuum and the solid residue was taken up in ether, washed successively with two portions of water, two portions of sodium bicarbonate solution, and two portions of brine and dried over anhydrous magnesium sulfate. The ether was removed under vacuum to yield a crude mixture of the two title compounds.

This mixture was separated by column chromatography on 600 g of silica gel, eluting with a 4:1 mixture of hexane-ethyl acetate.

The first fraction eluted was 5-(4-fluorophenyl)-1-(3-oxopropyl)-N,4-diphenyl-2-(trifluoromethyl)-1H-pyrrole-3-carboxamide.

The 90 MHz proton magnetic resonance spectrum of a deuterochloroform solution of this material exhibited signals at 2.73 (triplet, J=7 Hz, 2H); 4.21 (triplet, J=7 Hz, 2H); 6.7–7.3 (multiplet, 5H); 7.40 (singlet, 5H), and 9.43 (singlet, 1H) parts per million downfield from tetramethylsilane.

The second compound eluted from the column was 2-(4-fluorophenyl)-1-(3-oxopropyl)-N,4-diphenyl-5-(trifluoromethyl)-1H-pyrrole-3-carboxamide.

The 90 MHz proton magnetic resonance spectrum of a deuterochloroform solution of this material exhibited signals at 2.67 (triplet, J=7 Hz, 2H); 4.25 (triplet, J=7 Hz, 2H); 7.0–7.3 (multiplet, 14H); and 9.43 (singlet, 1H) parts per million downfield from tetramethylsilane.

Step C. Preparation of trans-2-(4-fluorophenyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-5-(trifluoromethyl)-pyrrole-3-carboxamide and trans-5-(4-fluorophenyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-2-(trifluoromethyl)-pyrrole-3-carboxamide

Employing the general methods detailed in Example 1, Steps G and H, the title compounds were prepared from the aldehyde compounds of this example, Step B.

The elemental analyses of the two title compounds were:

For trans-5-(4-fluorophenyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-2-(trifluoromethyl)-pyrrole-3-carboxamide:

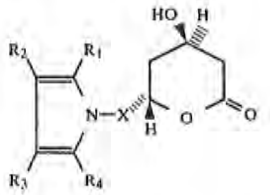
Analyzed for $C_{31}H_{26}N_2O_4$: Calc.: C, 65.72%; H, 4.63%; N, 4.94%; Found: C, 65.82%; H, 4.91%; N, 4.69%.

The trans-2-(4-fluorophenyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-5-(trifluoromethyl)-pyrrole-3-carboxamide was found, upon recrystallization from toluene to contain 0.25 mols of toluene as solvent of crystallization, mp 106°–111° C.

Analyzed for $C_{31}H_{26}N_2O_4.0.25C_7H_8$: Calc.: C, 66.72%; H, 4.79%; N, 4.72%; Found: C, 66.81%; H, 4.86%; N, 4.60%.

I claim:

1. A compound of structural formula I



wherein

X is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or $-CH_2CH(CH_3)-$;

R_1 is

1-naphthyl;
2-naphthyl;
cyclohexyl;
norbornenyl;
phenyl;
phenyl substituted with
fluorine,
chlorine,
bromine,
hydroxyl,
trifluoromethyl,
alkyl of from one to four carbon atoms,
alkoxy of from one to four carbon atoms, or
alkanoyloxy of from two to eight carbon atoms;

either of R_2 or R_3 is $-CONR_5R_6$ where R_5 and R_6 are independently

hydrogen;
alkyl of from one to six carbon atoms;
phenyl;
phenyl substituted with
fluorine,
chlorine,
bromine,
cyano,
trifluoromethyl, or
carboalkoxy of from three to eight carbon atoms;

and the other of R_2 or R_3 is

hydrogen;
alkyl of from one to six carbon atoms;
cyclopropyl;
cyclobutyl;
cyclopentyl;
cyclohexyl;
phenyl; or
phenyl substituted with
fluorine,
chlorine,
bromine,
hydroxyl,
trifluoromethyl,
alkyl of from one to four carbon atoms,
alkoxy of from one to four carbon atoms, or
alkanoyloxy of from two to eight carbon atoms;

R_4 is

alkyl of from one to six carbon atoms;
cyclopropyl;
cyclobutyl;
cyclopentyl;
cyclohexyl; or
trifluoromethyl;

or a hydroxy acid or pharmaceutically acceptable salts thereof, corresponding to the opened lactone

ring of the compounds of structural formula I above.

2. A compound as defined by claim 1 wherein X is $-CH_2CH_2-$.

3. A compound as defined by claim 2 wherein R_1 is phenyl; or phenyl substituted with fluorine, chlorine, bromine, hydroxyl; trifluoromethyl; alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms.

4. A compound as defined by claim 2 wherein R_4 is alkyl of from one to six carbon atoms.

5. A compound as defined by claim 1 having the name trans-(±)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide.

6. A compound as defined by claim 1 having the name trans-2-(4-fluorophenyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-5-trifluoromethyl-1H-pyrrole-3-carboxamide.

7. A compound as defined by claim 1 having the name trans-5-(4-fluorophenyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-2-trifluoromethyl-1H-pyrrole-3-carboxamide.

8. A pharmaceutical composition, useful as a hypocholesterolemic agent, comprising a hypocholesterolemic effective amount of a compound in accordance with claim 1 in combination with a pharmaceutically acceptable carrier.

9. A method of inhibiting cholesterol biosynthesis in a patient in need of such treatment by administering a pharmaceutical composition as defined by claim 8.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE EXTENDING PATENT TERM UNDER 35 U.S.C. § 156

PATENT NO.	:	4,681,893
ISSUED	:	July 21, 1987
INVENTOR(S)	:	Bruce D. Roth
PATENT OWNER	:	Warner-Lambert Company

This is to certify that there has been presented to the

COMMISSIONER OF PATENTS AND TRADEMARKS

an application under 35 U.S.C. § 156 for an extension of the patent term. Since it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

1,213 days

from May 30, 2006, the original expiration date of the patent, subject to the provisions of 35 U.S.C. § 41(b), with all rights pertaining thereto as provided by 35 U.S.C. § 156(b).

I have caused the seal of the Patent and Trademark Office to be affixed this 15th day of July 1998.

Bruce A. Lehman

Bruce A. Lehman
Assistant Secretary of Commerce and
Commissioner of Patents and Trademarks

US004681893C1

(12) EX PARTE REEXAMINATION CERTIFICATE (6392nd)

United States Patent
Roth

(10) Number: US 4,681,893 C1
(45) Certificate Issued: Aug. 26, 2008

(54) **TRANS-6-[2-(3- OR 4-CARBOXAMIDO-SUBSTITUTED PYRROL-1-YL)ALKYL]-4-HYDROXYPYRAN-2-ONE INHIBITORS OF CHOLESTEROL SYNTHESIS**

(75) Inventor: **Bruce D. Roth**, Ann Arbor, MI (US)

(73) Assignee: **Warner-Lambert Company**, Ann Arbor, MI (US)

Reexamination Request:
No. 90/008,727, Jul. 2, 2007

Reexamination Certificate for:
Patent No.: **4,681,893**
Issued: **Jul. 21, 1987**
Appl. No.: **06/868,867**
Filed: **May 30, 1986**

(51) **Int. Cl.**
C07D 405/00 (2006.01)
C07D 405/06 (2006.01)

(52) **U.S. Cl.** **514/422**; 514/423; 546/256; 546/279.1; 548/517; 548/537

(58) **Field of Classification Search** ..... None
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,634,453	A *	1/1972	McManus et al.	548/486
3,808,254	A	4/1974	Matthews	
3,931,173	A *	1/1976	Parker et al.	544/148
3,965,129	A	6/1976	Perry et al.	
3,983,140	A	9/1976	Endo et al.	
4,072,698	A	2/1978	Hylton et al.	
4,137,322	A	1/1979	Endo et al.	
4,139,555	A	2/1979	Zerbes	
4,171,359	A	10/1979	Weinstock	
4,192,872	A	3/1980	Weinstock	
4,231,938	A	11/1980	Monaghan et al.	
4,281,132	A	7/1981	Ward	
4,282,155	A	8/1981	Smith et al.	
4,293,496	A	10/1981	Willard	
4,319,039	A	3/1982	Albers-Schonberg	
4,342,761	A	8/1982	Ward	
4,342,767	A	8/1982	Albers-Schonberg et al.	
4,346,227	A	8/1982	Terahara et al.	
4,374,829	A	2/1983	Harris et al.	
4,374,844	A	2/1983	McCombie	
4,375,475	A	3/1983	Willard et al.	
4,444,784	A	4/1984	Hoffman et al.	
4,474,971	A	10/1984	Wareing	
4,495,103	A	1/1985	Terashima et al.	
4,555,511	A	11/1985	Schnorrenberg et al.	
4,581,453	A *	4/1986	Ippen et al.	544/331
4,611,067	A	9/1986	Volante et al.	
4,613,610	A	9/1986	Wareing	
4,647,576	A *	3/1987	Hoefle et al.	514/422
4,681,893	A	7/1987	Roth	
4,697,036	A	9/1987	Giordano et al.	
4,739,073	A	4/1988	Kathawala	
4,743,450	A	5/1988	Harris et al.	
4,775,681	A	10/1988	Heifetz	
4,786,505	A	11/1988	Lovgren et al.	
4,853,230	A	8/1989	Lovgren et al.	
4,898,868	A	2/1990	Bergmann et al.	
4,950,775	A	8/1990	Heathcock et al.	
4,962,115	A	10/1990	Van Daele	
4,976,949	A	12/1990	Meyer et al.	
4,978,791	A	12/1990	Völker et al.	
4,992,462	A	2/1991	Hubsch et al.	
5,003,080	A	3/1991	Butler et al.	
5,004,651	A	4/1991	Becker	
5,006,530	A	4/1991	Angerbauer et al.	
5,030,447	A	7/1991	Joshi et al.	
5,045,321	A	9/1991	Makino et al.	
5,055,484	A	10/1991	Jendralla et al.	
5,061,722	A	10/1991	Teetz et al.	
5,093,132	A	3/1992	Makino et al.	
5,097,045	A	3/1992	Butler et al.	
5,124,482	A	6/1992	Butler et al.	
5,149,837	A	9/1992	Butler et al.	
5,151,433	A	9/1992	Fulbreth et al.	
5,208,258	A	5/1993	Heathcock et al.	
5,216,174	A	6/1993	Butler et al.	
5,245,047	A	9/1993	Butler et al.	
5,273,995	A	12/1993	Roth	
5,280,126	A	1/1994	Butler et al.	
5,354,772	A	10/1994	Kathawala	
5,378,729	A	1/1995	Kohn et al.	
5,395,847	A	3/1995	Weinstock et al.	
5,969,156	A	10/1999	Briggs	
6,087,511	A	7/2000	Lin et al.	
6,121,461	A	9/2000	McKenzie et al.	
6,274,740	B1	8/2001	Lin et al.	
6,605,729	B1	8/2003	Byrn et al.	
5,969,156	C1	9/2006	Briggs et al.	
7,144,915	B2	12/2006	Byrn et al.	

FOREIGN PATENT DOCUMENTS

AU	601981	9/1990
AU	621874	3/1992
CA	1161380	1/1984
CA	1268768	5/1990
CA	1304080	6/1992
CA	1330441	6/1994
CA	2021546	4/1997
CA	2465565	12/2004
DK	0 171 588	12/1987
DK	171588 B1	2/1997
EP	0 024 348	3/1981

(Continued)

OTHER PUBLICATIONS

Reissue application and related papers, U.S. Appl. No. 11/653,830, filed Jan. 16, 2007 (Reissue of U.S. Patent 5,273,995).

(Continued)

Primary Examiner—Evelyn Huang

(57) **ABSTRACT**

Certain trans-6-[2-(3- or 4-carboxamido-substituted pyrrol-1-yl)alkyl]-4-hydroxypyran-2-ones and the corresponding ring-opened acids derived therefrom which are potent inhibitors of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase HMG CoA reductase and are thus useful hypolipidemic or hypocholesterolemic agents. Pharmaceutical compositions containing such compounds, and a method of inhibiting the biosynthesis of cholesterol employing such pharmaceutical compositions are also disclosed.

FOREIGN PATENT DOCUMENTS

EP	0 114 027 A1	7/1984
EP	0 171 588 A1	2/1986
EP	0179 559 A2 *	4/1986
EP	0 211 416	2/1987
EP	0 221 025 A1	5/1987
EP	0 232 997	8/1987
EP	0 247 633	12/1987
EP	0 251 625	1/1988
EP	0 259 086	3/1988
EP	0 319 856 A2	6/1989
EP	0 330 172	8/1989
EP	89103078.5	8/1989
EP	0 409 281	1/1991
IE	1197/87 L	11/1987
IE	890391	8/1989
JP	2240/1982	1/1982
JP	10572/1983	5/1983
JP	62-289577	12/1987
JP	72652/1988	4/1988
KR	1987-5372	2/1994
PT	84975	6/1987
PT	89774	10/1989
WO	WO 84/02131	6/1984
WO	WO 88/07582	10/1988
WO	WO 89/07598	8/1989
WO	WO 90/00553	1/1990
WO	WO 97/03959	2/1997
WO	WO 99/47138	9/1999

OTHER PUBLICATIONS

"Stipulated Amended Order of Final Judgement" dated Dec. 13, 2007 in Civil Action No. 07–138 (JJF), United States District Court for the District of Delaware.

Alberts Am.J.Cardiology vol. 62, 10J–15J (1988).

Alberts Proc Natl Acad Sci USA Jul. 1980;77(7):3957–61.

Ariëns et al. Cholinergic and Anticholinergic Drugs: Do they act on common receptors?, Ann NY Acad Sci, vol. 144, pp. 842–868 (1967).

Ariéns Stereochemistry and Biological Activity of Drugs, 11–53, 89–102, 161–185 (1983).

Ariéns Stereochemistry, a Basis for Sophisticated Nonsense in Pharmacokinetics and Clinical Pharmacology, Eur. J. Clin. Pharmacol., vol. 26, pp. 663–668 (1984).

Ariéns, E.J., "Implications of the Neglect of Stereochemistry in Pharmacokinetics and Clinical Pharmacology", Drug Intelligence and Clinical Pharmacy, (Oct. 1987), vol. 21, 827–829.

Ariéns, E.J., "Stereochemistry in the Analysis of Drug–Action. Part II.", Medicinal Research Reviews, (1987), vol. 7, No. 3, 367–387.

Ariéns, E.J., "Stereochemistry: A Source of Problems in Medicinal Chemistry", Medicinal Research Reviews, (1986), vol. 6, No. 4, 451–466.

Ariéns, Chirality in bioactive agents and its pitfalls, TIPS, Elsevier Publishers B.V., Amsterdam, p. 200–205 (1986).

Audebert Direct Resolution of Enantiomers in Column Liquid Chromatography, J. Liquid Chromatography, vol. 2, No. 8, 1063–1095 (1979).

Banitt, E.H. et al., "Resolution of Flecainide Acetate, N–(2–Piperidylmethyl)–2,5–bi5(2,2,2–trifluoroethoxy)benzamide Acetate, and Antiarrhythmic Properties of the Enantiomers", J. Med. Chem. (1986),29:299–302.

Berge et al. Pharmaceutical Salts, J. Pharm. Sci., vol. 66(1):1–19 (1977).

Braun, M et al., Tetrahedron Lett., 25, 5031–5034 (1984).

Brown, A.G. et al., "Crystal and Molecular Structure of Compactin, a New Antifungal Metabolite from *Penicillium brevicompactum*", J. Chem. Soc. Perkin I, (1976) 1165–1170.

Burger Medicinal Chemistry, Chapter 7, pp. 81–107 (1970).

Carey et al. "Advanced Organic Chemistry", 2nd Ed., Chapter 2 and p. 75 (1984).

Stinson Chemical and Engineering News, 70, Sep. 28, 46 (1992).

Stinson Chemical and Engineering News, 71, Sep. 27, 38 (1993).

Collet et al. Optical Resolution by Direct Crystallization of Enantiomer Mixtures, Chemical Reviews, vol. 80, No. 3, 215–230 (1980).

Conant et al. The Chemistry of Organic Compounds, A Year's Course in Organic Chemistry, 4th ed. Macmillan, New York, 1954, p. 234.

Cook Enantioselective Drug Analysis, Pharmacy International, vol. 6, No. 12, pp. 302–305 (1985).

Decamp Chirality, 1989, 1: 2–6.

Demerson et al. Resolution of Etodolac and Antiinflammatory and Prostaglandin Synthetase inhibiting Properties of the Enantiomers, J. Med. Chem., vol. 26, No. 12, 1778–1780 (1983).

Dotsevi, C. et al., "Chromatographic Optical Resolution through Chiral Complexation of Amino Ester Salts by a Host Covalently Bound to Silica Gel", J. Am. Chem. Soc., (1975), 97:1259–1261.

Dugan, R.E. et al., "Factors Affecting the Diurnal Variation in the Level of β–Hydroxy–β–Methylglutaryl Coenzyme A Reductase and Cholesterol–Synthesizing Activity in Rat Liver", Archiv. Biochem. Biophys., (1972), 152:21–27.

Eliel et al., Stereochemistry of Organic Compounds, Wiley, New York, 1994, pp. 329–331, and remainder of Section 7–3.

Eliel et al., Section 3–1—Compounds with One Asymmetric Carbon Atom, Stereochemistry of Carbon Compounds, McGraw–Hill Book Company, Inc. (1962).

Eliel et al., Section 4–4—Resolution of Racemic Modifications, Stereochemistry of Carbon Compounds, McGraw–Hill Book Company, Inc. pp. 47–74 (1962).

Endo, J Med Chem., 28: 401–405 (1985).

Endo, A. et al., "Biochemical Aspect of HMG CoA Reductase Inhibitors", Adv. in Enzyme Regulation, Proceedings of the 28 Symposium on Regulation of Enzyme Activity and Synthesis in Normal and Neoplastic Tissues held at Indiana University School of Medicine, Indianapolis, Indiana, (Oct. 2 and 3, 1988), vol. 28, p. 53–64.

Endo, A. et al., "Inhibition of Cholesterol Synthesis in vitro and in vivo by ML–236A and ML–236B, Competitive Inhibitors of 3–Hydroxy–3–methylglutaryl– Coenzyme A Reductase", Eur. J. Biochem., (1977), 77:31–36.

Endo, A., "Chemistry, Biochemistry, and Pharmacology of HMG–CoA Reductase Inhibitors", Klin. Wochenschr, (1988) 66:421–427.

Falck, J.R. et al., "Total Synthesis of (+)–Dihydromevinolin", Tetrahedron Letters, (1984), vol. 25, No. 33, pp. 3563–3566.

Fessenden et al. Section 4.10—Resolution of a Racemic Mixture, Organic Chemistry, 2nd Ed., Willard Grant Press, Boston (1982).

Fieser et al. Organic Chemistry, D. C. Heath, Boston, 2nd ed., 1950, pp. 267–274.

Fogassy, E. et al., "Pseudosymmetry and Chiral Discrimination in Optical Resolution via Diastereoisomeric Salt Formation. The Crystal Structures of (R)- and (S)-N-Methylamphetamine Bitartrates (RMERTA and SMERTA)", J. Chem. Soc. Perkin Trans. II, (1986) 1881–1886.
Gekkan-Yakuji, vol. 29, No. 10, pp. 23–26 (with English translation).
Goldman, M. et al., "Resolution of Chiral Olefinic Hydrocarbons and Sulfoxides by High-Performance Liquid Chromatography via Diastereomeric Platinum Complexes", J. Am. Chem. Soc., (1982) 104:1093–1095.
Gould, P.L., "Salt Selection for Basic Drugs", Int. J. Pharmaceutics, (1986), 33:201–217.
Greene Chapter 6—Preformulation, in Modern Pharmaceutics, Banker and Rhodes, Marcel Dekker Inc., New York.
Grieco, P.A. et al., "Convergent, Enantiospecific Total Synthesis of the Hypocholesterolemic Agent (+)—Compactin", J. Am. Chem. Soc., (1986) 108:5908–5919.
Grieco, P.A. et al., "Total Synthesis of the Hypocholesterolemic Agent (+)—Compactin", J. Am.Chem. Soc., (1983), 105:1403–1404.
Grundy, S.M., "HMG-CoA Reductase Inhibitors for Treatment of Hypercholesterolemia", N.E. J. Med., (Jul. 7, 1988), vol. 319, No. 1, pp. 24–33.
Guindon, Y. et al., "Preparation of ethyl 5(S),6-epoxy-3(R)-(methyoxmethoxy)hexanoate: A key chiral intermediate for mevinolin and compactin", Tetrahedron Letters, (1985), vol. 26, No. 9, pp. 1185–1188.
Heathcock et al. J. Med. Chem. 1987, 30, 1858–1873.
Heathcock et al. J. Med. Chem. 1989, 32, 197–202.
Helmchen et al, Agnew Chem. Int. Edn. 1979. 18, p. 63–65.
Hirama M. et al., "Chiral Total Synthesis of Compactin", J. Am. Chem. Soc., (1982), 104:4251–4253.
Hirama, M. et al., "Total Synthesis of (+)-Monacolin K (Mevinolin)", Tetrahedron Letters, (1983), vol. 24, No. 17, pp. 1811–1812.
Hoeg, J.M. et al., "3.-Hydroxy-3-Methylglutaryl-Coenzyme A Reductase Inhibitors in the Treatment of Hypercholesterolemia", JAMA, (Dec. 25, 1987), vol. 258, No. 24, p. 3532–3536.
Hoffman et al, J. Med. Chem., 29: 159–169 (Feb. 1986).
Hoffman, W.F. et al., "3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors. 4. Side Chain Ester Derivatives of Mevinolin", J. Med. Chem. (1986) 29:849–852.
Hsu, C-T, et al., "Total Synthesis of the Hypocholesterolemic Agent Compactin", J. Am. Chem.Soc., (1983), 105:593–601.
Hubbard et al. Chiral Pharmacology and its Consequences for Therapeutic Monitoring, Clin. Biochem., vol. 19, pp. 107–112 (1986).
Jackson et al. Characterization and Antifertility Activity in Rats of S(+) a-Chlorohydrin Chem.-Biol Interactions, vol. 17, No. 1, 117–120 (1977).
Jacques et al Enantiomers, Racemates, and Resolutions, John Wiley & Sons, Toronto (1981).
Jacques et al. Types of Crystalline Racemates, Enantiomers, Racemates, and Resolutions, c.1, 3–23 (1981).
Jacques et al. Formation and Separation of Diastereomers, Enantiomers, Racemates, and Resolutions, c.5, 251–281 (1981).
Jacques et al Section 5.1.2—Resolution of Bases, Enantiomers, Racemates, and Resolutions, John Wiley & Sons, Toronto (1981).
Jacques et al. Experimental Aspects and Art of Resolutions, Enantiomers, Racemates, and Resolutions, c.7, 378–434 (1981).
Johnson et al. Tetrahedron Letters, vol. 29, No. 31, pp. 3757–3760, 1988.
Kalant et al Chapter 9—Drug Receptors, Principles of Medical Pharmacology, 4th ed,, University of Toronto Press, Toronto (1985).
Kalant et al Chapter 10—Specificity of Drug Action, Principles of Medical Pharmacology, 4th ed,, University of Toronto Press, Toronto (1985).
Kaneko et al. Eur. J. Biochem., 87:313–321 (1978).
Kathawala, F.G., "Exciting Developments in the Area of HMG-CoA Reductase Inhibitors", Trends in Medicinal Chemistry '88: Proceedings of the Xth International Symposium on Medicinal Chemistry, Budapest, Aug. 15–19, 1988, (disclosed at the conference in Aug. 1988), pp. 709–728 (textbook received at CISTI on Jun. 23, 1989).
Kemp et al. Organic Chemistry, Worth, New York, 1980, pp. 172 and 173.
Kim, Y.H. et al., Chiral Differentiation by the P-(+)-Hexahelicene-7-7'-dicarboxylic Acid Disodium Salt. Resolution of N-2,4-Dinitrophenyl-α-amino-acid Esters by High Performance Liquid Chromatography, J. Chem. Soc., Chem. Commun., (1982), p. 1336–1337.
Krause et al. Atherosclerosis, 117:237 (1995).
Lee, TIPS, 8:442–446 (1987).
Lee, T-J, "An expeditious chiral route to analogs of mevinolin and compactin", Tetrahedron Letters, (1985), vol. 26, No. 41, pp. 4995–4996.
Lee, T-J, et al., "Structural Modification of Mevinolin", J. Org. Chem., (1982), 47:4750–4757.
Lehmann et al. Stereoselectivity and Affinity in Molecular Pharmacology, Jucker, E. (ed), Progress in Drug Research, vol. 20, Birkhauser, Basel Stuttgard, pp. 101–142.
Lehmann Stereoselective Molecular Recognition in Biology. Cuatrecasas, P., Greaves M.F. (eds), Receptors and Recognition, vol. 5, Series A, Chapman and Hall, London, pp. 1–77 (1978).
Lim et al. Enantiomeric resolution of di-threo-methylphenidate, U.S.P. (Ritalin®), by high- performance liquid chromatography, J. Chromatography, vol. 328, 378–386 (1985).
Liu et al. Effect of Enantiomeric Purity on Solubility Determination of Dexclamol Hydrochloride, J. Pharm. Sci., vol. 67, pp. 636–638 (1978).
Lynch et al., Tetrahedron Letters, 28: 1385–1388 (1987).
Majewski et al. Tetrahedron Letters, vol. 25, No. 20 pp. 2101–2104, 1984.
Mantell, G., "Lipid Lowering Drugs in Atherosclerosis—The HMG-CoA Reductase Inhibitors", Clin. and Exper. Hyper.-Theory and Practice, (Jan. 1, 1989), vol. 11, Issue 5–6, 927–941.
March Methods of Resolution, in Advanced Organic Chemistry—Reactions, Mechanisms and Structure, 2nd Ed., McGraw Hill, New York 1977, pp. 108–111.
Martindale, The Extra Pharmacopoeia (ed. Reynolds 28th ed. 1982), p. 44.
McBlain et al. Facile Route to the Resolution of the Enantiomers of 1-Chloro-2-[2,2,2-trichloro-1-(4-chlorophenyl) ethyl]benzene (o,p'-DDT), J. Ag. Food Chem., vol. 25, No. 1, 59–63 (1977).

Meyers, A.I., et al., "Separation of Diastereomers Using a Low Cost Preparative Medium–Pressure Liquid Chromatograph", J. Org. Chem., (1979), vol. 44, No. 13, p. 2247–2249.

Morrison et al Section 7.9—Reactions of chiral molecules with optically active reagents. Resolution, Organic Chemistry, 3rd Ed., Allyn and Bacon, Inc., Boston (1973).

Nakamura et al. Biochemistry, 24:1364–1376 (1985).

Narasaka et al. Tetrahedron, 40, 223–2238 (1984).

Pirkle, W.H. et al., "Broad Spectrum Methods for the Resolution of Optical Isomers. A Discussion of the Reasons Underlying the Chromatographic Separability of Some Diastereomeric Carbamates", J. Org. Chem,(1977), vol. 42, No. 11, p. 1839–1844.

Portoghese Relationships between Stereostructure and Pharmacological Activities, Elliott, H.W., Cutting, W.C., Dreisbach, R.H. (eds), Annual Review of Pharmacology, vol. 10, Annual Reviews Inc., Palo Alto, CA, pp. 51–76 (1970).

Prasad, K. et al., "Asymmetric synthesis of (3R–trans)– and (3S–cis)–hydroxy–5–pentanolides", Tetrahedron Letters, (1984), vol. 25, No. 32, pp. 3391–3394.

Prugh et al., Tetrahedron Letters 23: 281–284 (1982).

Ravin Chapter 75—Preformulation, Remington's Pharmaceutical Sciences, 16th Ed., Philadelphia College of Pharmacy and Science (1980).

Repta et al. Utilization of an Enantiomer as a Solution to a Pharmaceutical Problem: Application to Solubilization of 1,2–Di(4–piperazine–2,6–dione)Propane, J. Pharm. Sci., vol. 65, pp. 238–242.

Robinson Absolute configurations of(−+−)– and (−)–1–amino 3–chloropropan–2–ol hydrochlorides, Chemistry and Industry, No. 15, p. 652 (1976).

Rosen, T. et al., "Tetrahedron Report No. 208—The Synthesis of Mevinic Acids", Tetrahedron, (1986), vol. 42, No. 18, pp. 4909–4951.

Roth et al. Tetrahedron Letters, vol. 29, No. 11, pp. 1255–1258 (1988).

Roth, Progress In Med. Chem., 40, 1–22 (2002).

Saigo, K. et al., "Optical Resolution of 2–Amino–1,2–diphenylethanol by Preferential Crystallization and Its Utilization in Fractional Crystallization and Enantioselective Reduction of Prochiral Ketones", Bull.Chem. Soc. Jpn., (1982) 55:1568–1573.

Schneider, C.S. et al., "Dopamine Autoreceptor Agonists: Resolution and Pharmacological Activity of 2,6–Diaminotetrahydrobenzothiazole and an Aminothiazole Analogue of Apomorphine", J. Med. Chem., (1987), 30:494–498.

Serizawa, N. et al., "Microbial Hydroxylation of ML–236B (Compactin) and Monacolin K (MG–530B)", J. Antibiotics, (May 1983), 36:604–607.

Shaw, CDER FDA Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances (1987).

Slater, E.E. et al., "Mechanism of Action and Biological Profile of HMG CoA Reductase Inhibitors, A New Therapeutic Alternative", Drugs, (1988) 36 (Suppl. 3):72–82.

Sletzinger, M. et al., "A Diastereospecific, Non–Racemic Synthesis of a Novel β–Hydroxy–σ–Lactone HMG–CoA Reductase Inhibitor", Tetrahedron Letters, (1985), vol. 26, No. 25, pp. 2951–2954.

Stokker et al., J. Med Chem 28:347–358 (1985).

Stokker et al. J. Med. Chem. 1986, 29, 170–181.

Stokker et al. J. Org. Chem, 1986, 51, 4931–4934.

Stokker, G.E. et al., "3–Hydroxy–3–methylglutaryl– coenzyme A Reductase Inhibitors. 5. 6–(Fluoren–9–yl)– and 6–(fluoren–9–ylidenyl)–3,5–dihydroxyhexanoic acids and their lactone derivatives", J. Med. Chem., (May 1986), 29(5):852–855.

Streitwieser et al., Introduction to Organic Chemistry, Macmillan, New York, 3rd ed. 1985, p. 695.

Streitwieser Jr., A., "Stereoisomerism", Introduction to Organic Chemistry, Macmillan, New York, 3rd ed. 1985 Chapter 7, pp. 113–139.

Takano et al. Synthesis, Jul. 1989, vol. 7, p. 539–541.

The Merck Index, 10th Ed., (1983), entry 5949. N–Methylglucamine, p. 870–871.

The Merck Index, 12th Ed., (1996), entry 897. Atorvastatin, p. 146.

Tobert, J.A., "New developments in lipid–lowering therapy: the role of inhibitors of hydroxymethylglutarylcoenzyme A reductase", Circulation, (1987), 76, No. 3, 534–538.

Viret et al. Simple Optical Resolution of Terleucine, Tetrahedron Letters, vol. 27, No. 48, pp. 5865–5868 (1986).

Vollhardt Section 5–7—Resolution: The Separation of Enantiomers, in Organic Chemistry, W.H. Freeman and Company, New York (1987).

Vriesema, B.K. et al., "Resolution of 2–amino–5–thiomethyl pentanoic acid (homomethionine) with aminopeptidase from *pseudomonas putida* or chiral phosphoric acids.", Tetrahedron Letters, (1986), vol. 26, No. 18, p. 2045–2048.

Walking, D. et al., "Decision Analysis in Drug Product Development", Drug & Cosmetic Industry, (1973) 112(3):39–41.

Weissbuch, I. et al., "Design of Polymeric Inhibitors for the Control of Crystal Polymorphism. Induced Enantiomeric Resolution of Racemic Histidine by Crystallization at 25° C.", J. Am. Chem. Soc., (1987) 109:1869–1871.

Wells Pharmaceutical Preformulation: The Physicochemical Properties of Drug Substances—Chapter 2 (1988).

Whilen Topics in Stereochemistry, 6, 107–176 (1971).

Wilen et al. Tetrahedron, 33, 2725–2736 (1977).

Williams, K.M., "Chirality: Pharmacokinetics and Pharmacodynamics in 3 Dimensions", Clinical and Experimental Pharmacology and Physiology, (Jun. 1989), vol. 16, No. 6, pp. 465–470.

Witiak et al., Pharmaceuticals, Optically Active, Encyclopedia of Chemical Technology, 3ed, vol. 17, 311–345 (1982).

Wong, C–H. et al., "Mutual Resolution of (±)–ephedrine and Z–DL–Amino Acid Induced by Seeding Chiral Salt", Tetrahedron Letters No. 40, (1978), pp. 3813–3816.

Yang, Y–L., et al., "Mevinic Acids and Analogues: Preparation of a Key Chiral Intermediate", Tetrahedron Letters, (1982), vol. 23, No. 42, pp. 4305–4308.

Yoshino et al. Diabetes Research and Clinical Practice 2 (1986) 179–181.

Pfizer Inc, et al. v. *Ranbaxy Pharmaceuticals Limited, et al.*, 457 F. 3d 1284 (Fed. Cir. 2006) (Exhibit 1 to Preliminary Amendment in copending U.S. Appl. No. 11/653,830).

Pfizer Inc, et al. v. *Ranbaxy Pharmaceuticals Limited, et al.*, 405 F. Supp. 2d 495 (D. Del. 2005) (Exhibit 2 to Preliminary Amendment in copending U.S. Appl. No. 11/653,830).

"Pfizer's Proposed Findings of Fact", CA No. 03–209–JJF (Exhibit 3 to Preliminary Amendment in copending U.S. Appl. No. 11/653,830).

"Pfizer's Proposed Supplemental Findings of Fact", CA No. 03–209–JJF (Exhibit 4 to Preliminary Amendment in copending U.S. Appl. No. 11/653,830).
"Pfizer's Proposed Conclusions of Law", CA No. 93–209–JJF (Exhibit 5 to Preliminary Amendment in copending U.S. Appl. No. 11/653,830).
"Pfizer's Proposed Supplemental Conclusion of Law", CA No. 03–209–JJF (Exhibit 6 to Preliminary Amendment in copending U.S. Appl. No. 11/653,830).
"Opening Proposed Findings of Fact and Conclusions of Law of Defendants Ranbaxy Laboratories Limited and Ranbaxy Pharmaceuticals Inc.", CA No. 03–209–JJF (Exhibit 7 to Preliminary Amendment in copending U.S. Appl. No. 11/653,830).
"Petition for Panel Rehearing and Petition for Rehearing En Banc by Defendants–Appellants Ranbaxy Laboratories Limited and Ranbaxy Pharmaceuticals Inc." No. 2006–1179 (Exhibit 8 to Preliminary Amendment in copending U.S. Appl. No. 11/653,830).
"Plantiff–Appellee's Response to Petition for Rehearing and Rehearing En Banc", No. 2006–1179 (Exhibit 9 to Preliminary Amendment in copending U.S. Appl. No. 11/653,830).
"Order" denying Request for Panel Rehearing ad Rehearing En Banc (Exhibit 10 to Preliminary Amendment in copending U.S. Appl. No. 11/653,830).
"Pfizer's Post–Trial Opening Brief", CA No. 03–209–JJF (Exhibit 11 to Preliminary Amendmen in copending U.S. Appl. No. 11/653,830).
"Opening Post–Trial Brief of Defendants Ranbaxy Laboratories Limited and Ranbaxy Pharmaceuticals Inc.", CA No. 03–209–JJF (Exhibit 12 to Preliminary Amendment in copending U.S. Appl. No. 11/653,830).
"Pfizer's Corrected Post–Trial Reply Brief", CA No. 03–209–JJF (Exhibit 13 to Preliminary Amendment in copending U.S. Appl. No. 11/653,830).
"Defendant Ranbaxy Laboratories Limited's and Ranbaxy Pharmaceuticals Inc.'s Opposition Post–Trial Brief", CA No. 03–209–JJF (Exhibit 14 to Preliminary Amendment in copending U.S. Appl. No. 11/653,830).
Summaries of Non–United States Proceedings Involving Counterparts to U.S. Pat. No. 5,273,995, including: i) List of Countries (3 sheets); ii) Table of Foreign Lawsuits (5 sheets); and iii) Lipitor Canada Enantiomer Cases Document Schedules (28 sheets) (Exhibits 15, 15A and 15B in copending U.S. Appl. No. 11/653,830).
"Brief of Defendants–Appellants Ranbaxy Laboratories Limited and Ranbaxy Pharmaceuticals, Inc." No. 06–1179 (Exhibit 16 to Preliminary Amendment in copending U.S. Appl. No. 11/653,830).
"Brief of Plaintiffs–Appellees, Pfizer Inc." No. 06–1179 (Exhibit 17 to Preliminary Amendment in copending U.S. Appl. No. 11/653,830).
"Reply Brief of Defendants–Appellants Ranbaxy Laboratories Limited and Ranbaxy Pharmaceuticals, Inc." No. 06–1179 (Exhibit 18 to Preliminary Amendment in copending U.S. Appl. No. 11/653,830).
Sanofi–Synthelabo et al. v. *Apotex, Inc. et al.*, No. 06–1613 (Fed. Cir. Dec. 8, 2006) (Exhibit 20 to Preliminary Amendment in copending U.S. Appl. No. 11/653,830).
US 5,273,995 prosecution history, marked as Defendant's Trial Exhibit 139 in CA No. 022–209 (D. Del.) and comprising pages stamped RA0147320–RA014884 (Exhibit 22 to Preliminary Amendment in copending U.S. Appl. No. 11/653,830).
CA 1,330,441 file history which includes Canadian Patent Application No. 590,367 as filed Feb. 7, 1989.
CA 2,021,546 file history.
European Patent Application 87 107 847.3 file history.
European Patent Application 90 113 986.5 Claims (part of EP 0409281 file history C152).
European Patent Application 90 113 986.5 Claims as granted (part of EP 0409281 file history C152).
European Patent Application 90 113 986.5 (Jan 25, 2000 Communication) (part of EP 0409281 file history C152).
European Patent Application 90 113 986.5 Refusal (Sep. 5, 1998) (part of EP 0409281 file history C152).
European Patent Application 90 113 986.5 file history.
EP 0409281 file history.
US 4,618,893 file history.
US 5,003,080 file history.
"Petition for a Writ of Certiorani," *Ranbaxy Laboratories Limited et al.* v. *Pfizer Inc. et al.*, No. 06–1179, Jan. 22, 2007. (Exhibit 23 to Supplemental Communication in copending U.S. Appl. No. 11/653,830).
Pfizer Opposition to Ranbaxy Petition for Certiorani, Feb. 26, 2007. (Exhibit 24 to Supplemental Communication in copending U.S. Appl. No. 11/653,830).
Hall and Roush, *J. Org. Chem.*, 47: 4611–4621 (1982).
Roush and Gillis, *J. Org. chem.*, 47: 4825–4829 (1982).
Sit et al, *J. Med. Chem.*, 33:2982 (1990).
Amin et al., *J. Pharmacology* 46:13 (1993).
Underberg et al., *J. Pharm. Biomed Anal.* 8(8–12): 681–683 (1990).
Stinson, *Chemical and Engineering News*, 70(39): 46–79 (1992).
Stinson, *Chemical and Engineering News*, 71(39): 38–64 (1993).
Burlinson, *Tablets and Tabletting*, William Heinemann medical Books Ltd.: London, 1968.
Casy, A.F. Stereochemistry and Biological Activity. *Medicinal Chemistry*, Wiley: New York, 1970.
Rawlings, *Bentley's Textbook of Pharmaceutics*, 8th Ed., Bailliere Tindall: London, 1977.
Seeman, P. Drug Receptors. Kalant H. et al. eds., *Principles of Medical Pharmacology*, 4th Edition, University of Toronto Press: Toronto, 1985.
Lachman et al., Proformulation. *The Theory and Practice of Industrial Pharmacy*, 3rd Edition, Lea & Febiger: Philadelphia, 1986.
Lieberman et al., eds. *Pharmaceutical Dosage Forms Tablets*, 2nd Edition (vol. 1), Marcel Dekker: New York, 1989.
Gennaro, *Remington's Pharmaceutical Sciences*, 18th Ed., Mack Printing Company: Easton, Pennsylvania, 1990.
Banker, Rhodes, eds., *Modern Pharmaceutics*, 3rd Edition, Marcel Dekker, Inc.: New Yor, 1996.
Kibbe, A.H., ed., *Handbook of Pharmaceutical Excipients*, 3rd Ed., Pharmaceutical Press: London, 2000.
The Merck Index, 10th Edition (1983), entry 5949: *N-Methylglucamine*, pp. 870–871.
The Merck Index, 12th Edition (1996), entry 897: *Atorvastatin*, p. 146.
Transcript of evidence given by Dr. Scallen in US trial of *Pfizer, Inc., et al.* v. *Ranbaxy Laboratories Limited et al.*, Court file No. 03–209–JJF, on Dec. 3, 2004.
Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances, Feb. 1987.

Stein et al., The Lovastatin–Niacin Trial: Effects on Lipoproteins. *Arteriosclerosis and Thrombosis* 11: 1458a (1991).

Dujovne et al ., The Lovastatin–Niacin Trial: Adverse Events. *Arteriosclerosis and Thrombosis* 11: 1458a (1991).

Frost, P.H. et al., Lipid Metabolism. In PA Fitzgerald, Ed., *Handbook of Clinical Endocrinology*, 2nd Edition, Appleton and Lange, 1991.

Frost, P.H. et al., Lovastatin–Niacin Comoparative Trial. *JACC* 19, 374A, 1992.

Lovastatin Study Groups I through IV. Lovastatin 5–year safety and efficacy study. *Arch. Intern. Med.* 153: 1079–1087 (1993).

Illingworth, D.R. et al., Comparative effects of lovastatin and niacin in primary hypercholesterolemia: A prospective trial. *Arch. Intern. Med.* 154: 1586–1595 (1994).

Stein, E.A. et al., Efficacy and tolerability of low–dose simvastatin and niacin, alone and in combination, in patients with combined hyperlipidemia: a prospective trial. J. *Cardiovasc. Pharmacol. Therapeut.* 1: 107–116 (1996).

Frost, P.H. et al., Rationale for use of non–high–density lipoprotein cholesterol rather than low–density lipoprotein cholesterol as a tool for lipoprotein cholesterol screening and assessment of risk and therapy. *Am. J. Cardiol.* 81: 26B–31B (1998).

Havel, R.J. et al., The role of non–high–density lipoprotein cholesterol in evaluation and treatment of lipid disorders. *J. Clin. Endocrinology and Metabolism* 85: 2105–2108 (2000).

The Cholesterol Myth, *Atlantic Monthly*, Sep. 1989.

National Cholesterol Education Program Guideline III (2004 Update).

Results of the National Cholesterol Education (NCEP) Program Evaluation Project Utilizing Novel E–Technology (Neptune) II Survey and Implications for Treatment under Recent NCEP Writing Group Recommentations.

Chaper 1—Selling to Everyone High Cholesterol. In Moynihan R. and Cassels A., *Selling Sickness*, Avalon Publishing Group: 2005, pp. 1–21.

Letter dated Dec. 2, 2005 from Taylor Wessing to L. Caswell attaching expert reports of Dr. Newton dated May 27, 2005 and Jun. 17, 2005 that were filed in *Ranbaxy (UK) Limited* v. *Warner–Lambert Company*, HC–04C 02167, and said reports.

Trial transcripts taken on Jul. 18 to 22, 2005 and Jul. 25, 2005 in *Ranbaxy (UK) Limited* v. *Warner–Lambert Company*, HC–04C 02167.

Warner–Lambert Company Notices of Application court files T–507–05, T–1128–05.

English translation of Austrian decisions invalidating Austrian Patent No. 207,896.

Lipitor advertising placed in the Canadian Medical Association Journal, from 1997 to 2005.

Consensus Conference. Lowering Blood Cholesterol to Prevent Heart Disease. *JAMA* 253: 1080–2086 (1985).

Report on the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. The Expert Panel. *Arch. Intern. Med.* 148: 36–69 (1988).

Canadian Consensus Conference on Cholesterol. Final Report, Canadian Consensus Conference on the Prevention of Heart and Vascular Disease by Altering Serum Cholesterol and Serum Lipoprotein Factors. *CMAJ* 139: 111–63 (1988).

Frolich et al., Rationale for and Outline of the Recommendations of the Working Group of Hypercholesterolemia and Other Dyslipidemias: Interim Report. *Can. J. Cardiol.* 14 (supp. A): 17A–21A (1988).

Fodor et al., for the Working Group on Hypercholesterolemia and Other Dyslipidemias: Recommendations for the Management and Treatment of Dyslipidemia. CMAJ 162 (10): 1441–1447 (2000).

Fodor et al., Recommendations for the management of dyslipidemia and the prevention of cardiovascular disease: 2003 update. *CMAJ* 168 (9): 921–924 (2003).

NHLBI News Release May 15, 2001, http://www.nhlbi.nih.gov/new/press/01–05–15.htm.

Manuel et al., The 2003 Canadian Recommendations for Dyslipidemia Management: Revisions are Needed. *CMAJ* 172: 1027–1032 (2005).

Documents compiled by the World Health Organization's Department of Essential Drugs & Medicines Policy published as http://www.drugpromo.info/read–reviews.asp?id=4 and http://www.drugpromo.info/read–reviews.asp?id=5.

Wazana, A., *JAMA* 283(3): 373–380 (2000).

Brophy et al., Statin wars following coronary revascularization—Evidence based clinical practice? *Can. J. Cardiol.* 22(1): 54–58 (2006).

Havel et al., A multicenter study of mevinolin (lovastatin) in treatment of heterozygous familial hypercholesterolemia. *Annals Int. Med.* 107: 609 (1987).

Lovastatin Study Group III. A multicenter comparison of lovastatin and cholestyramine in the therapy of severe primary hypercholesterolemia. *JAMA* 260: 359 (1988).

Defendants' Trial Exhibit 3323, "Data Provided to Patent Office in '995 Specification and Data from Experiment 107," from *Pfizer, Inc et al.* v. *Ranbaxy Laboratories Limited, et al.*, US District Court, District of Delaware, 03–209–JJF.

Defendants' Trial Exhibit 3325 from *Pfizer, Inc et al.* v. *Ranbaxy Laboratories Limited, et al.*, US District Court, District of Delaware, 03–209–JJF.

Defendants' Trial Exhibit 3325A from *Pfizer, Inc et al.* v. *Ranbaxy Laboratories Limited, et al.*, US District Court, District of Delaware, 03–209–JJF.

Dietschy 1, CSI IC_{50} values, from *Pfizer, Inc et al.* v. *Ranbaxy Laboratories Limited, et al.*, US District Court, District of Delaware, 03–209–JJF.

Dietschy 2, COR IC_{50} values, from *Pfizer, Inc et al.* v. *Ranbaxy Laboratories Limited, et al.*, US District Court, District of Delaware, 03–209–JJF.

Dietschy 3, IC_{50} values (nM) for head–to–head CSI and COR screens, from *Pfizer,, Inc et al.* v. *Ranbaxy Laboratories Limited, et al.*, US District Court, District of Delaware, 03–209–JJF.

Dietschy 4, AICS data, from *Pfizer, Inc et al.* v. *Ranbaxy Laboratories Limited, et al.*, US District Court, District of Delaware, 03–209–JJF.

Defendants' Trial Exhibit 319 from *Pfizer, Inc et al.* v. *Ranbaxy Laboratories Limited, et al.*, US District Court, District of Delaware, 03–209–JJF.

Defendants' Trial Exhibit 321 from *Pfizer, Inc et al.* v. *Ranbaxy Laboratories Limited, et al.*, US District Court, District of Delaware, 03–209–JJF.

Roth et al., Inhibitors of cholesterol biosynthesis. 3. Tetrahydro-4-hydroxy-6-[2-(1H-pyrrol-1-yl)ethyl]-2H-pyran-2-one inhibitors of HMG-CoA reductase. 2. Effects of introducing substituents at positions three and four of the pyrrole nucleus. *J. Med. Chem.* 34(1): 357-366 (Jan. 1991).

Warner-Lambert Pharmaceutical Research Report No. RR-740-02620, Acute Inhibition of Cholesterol Synthesis in the Rat by the Calcium Salts (Racemic and Chiral) of CI-971, dated May 31, 1989, identified as DTX 11 in *Pfizer, Inc et al.* v. *Ranbaxy Laboratories Limited, et al.*, US District Court, District of Delaware, 03-209-JJF.

Warner-Lambert/Parke-Davis memo to Oberkfell and Pieroni from Newton and Roth re: PD 134298-38A Product Profile A for HMG-Co-A Reductase Inhibitor, Jun. 1, 1989, identified as DTX 142 in *Pfizer, Inc et al.* v. *Ranbaxy Laboratories Limited, et al.*, US District Court, District of Delaware, 03-209-JJF.

Warner-Lambert/Parke-Davis Pharmaceutical Research Report RR-740-01682, CSI (Cholesterol Synthesis Inhibitors): A Rapid Screen for Inhibitors of Cholesterol Synthesis in Crude Microsomal Preparations from Rat Liver, dated May 3, 1985, identified as DTX 271 in *Pfizer, Inc et al.* v. *Ranbaxy Laboratories Limited, et al.*, US District Court, District of Delaware, 03-209-JJF.

Parke-Davis Memo re: Lead Compound Pharmacological Profile for CI-981 (PD 134298-38A) to Mr. H.F. Oberkfell and Mr. J. Peroni from Newton and Roth, dated Sep. 28, 1989, identified as DTX 4 in *Pfizer, Inc et al.* v. *Ranbaxy Laboratories Limited, et al.*, US District Court, District of Delaware, 03-209-JJF.

Chemist's Binder of Biological Data, identified as DTX 552, in *Pfizer, Inc et al.* v. *Ranbaxy Laboratories Limited, et al.*, US District Court, District of Delaware, 03-209-JJF.

CI-981 IND submitted to the FDA, identified as DTX 326 in *Pfizer, Inc et al.* v. *Ranbaxy Laboratories Limited, et al.*, US District Court, District of Delaware, 03-209-JJF.

SIT et al., Synthesis, Biological Profile, and Quantitative Structure Activity Relationship of a Series of Novel 3-Hydroxy-3-methylglutaryl Coenzyme A Reductase Inhibitors. *J. Med. Chem.* 33: 2982-2999 (1990).

Warner-Lambert/Parke-Davis Pharmaceutical Research Report No. RR967-01212, PD 123832 (Anti-Atherosclerosis)—Preformulation Summary, identified as DTX 28 in *Pfizer, Inc et al.* v. *Ranbaxy Laboratories Limited, et al.*, US District Court, District of Delaware, 03-209-JJF.

Warner-Lambert Report, "Atherosclerosis Drug Discovery Team Report," Dec. 12, 1989, referred to at paragraph 351 of *Ranbaxy Australia Pty Ltd* v. *Warner-Lambert Company LCC (No. 2)*, [2006]FCA 1787.

Warner-Lambert internal report dated Dec. 15, 1987, summarizing results of CSI 107, referred to at paragraph 291 of *Ranbaxy Australia Pty Ltd* v. *Warner-Lambert Company LCC (No. 2)*, [2006]FCA 1787.

Warner-Lambert internal memorandum dated Dec. 5, 1989, referred to at paragraph 341 of *Ranbaxy Australia Pty Ltd* v. *Warner-Lambert Company LCC (No. 2)*, [2006]FCA 1787.

Forms IV. Lists for Atorvastatin Calcium in Canada.

US Orange Book entries for atorvastatin.

Letter of Aug. 19 1998 from US PTO to Francis J. Tinney regarding patent extension for Lipitor.

Letter of Nov. 7, 2005 from William Curatolo of Pfizer Global Research & Development and Stephen R Byrn of SSCI, Inc. to the Division of Dockets Management, food and Drug Administration, entitled Citizen Petition.

NOC listings for rosuvastatin, fluvastatin, pravastatin, lovastatin, atorvastatin, sinvastatin, cerivastatin.

Ranbaxy Reply in Support of Petition for Certiorari (Exhibit 25 to Supplemental Communication in copending U.S. Appl. No. 11/653,830).

Supreme Court decision denying Certiorari (Exhibit 26 to Supplemental Communicationin copending U.S. Appl. No. 11/653,830).

Ranbaxy's Apr. 12, 2007 ANDA Notice Letter (Exhibit 27 to Supplemental Communication in copending U.S. Appl. No. 11/653,830).

Pfizer Complaint (138 Delaware Action) (Exhibit 28 to Supplemental Communication in copending U.S. Appl. No. 11/653,830).

Ranbaxy Amended Answer and Counterclaims (138 Delaware Action) (Exhibit 29 to Supplemental Communication in copending U.S. Appl. No. 11/653,830).

Pfizer Reply to Ranbaxy's Amended Answer (138 Delaware Action) (Exhibit 30 to Supplemental Communication in copending U.S. Appl. No. 11/653,830).

Pfizer Briefs in Support of Motions to Dismiss (138 Delaware Action) (Exhibit 31 to Supplemental Communication in copending U.S. Appl. No. 11/653,830).

Ranbaxy Responses to Motions to Dismiss (138 Delaware Action) (Exhibit 32 to Supplemental Communication in copending U.S. Appl. No. 11/653,830).

Teva ANDA Notice Letter (Exhibit 33 to Supplemental Communication in copending U.S. Appl. No. 11/653,830).

KSR decision (Exhibit 34 to Supplemental Communication in copending U.S. Appl. No. 11/653,830).

Commissioner's Memorandum re: KSR decision (Exhibit 35 to Supplemental Communication in copending U.S. Appl. No. 11/653,830).

Pfizer v. *Apotex* decision (Exhibit 36 to Supplemental Communication in copending U.S. Appl. No. 11/653,830).

Order Denying Rehearing, and Dissents, in *Pfizer* v. *Apotex* decision (Exhibit 37 to Supplemental Communication in copending U.S. Appl. No. 11/653,830).

Danish decision, English translation (Exhibit 38 to Supplemental Communication in copending U.S. Appl. No. 11/653, 830).

Australian decision, *Ranbaxy Australia* v. *Warner-Lambert Co. LLC* (Exhibit 39 to Supplemental Communication in copending U.S. Appl. No. 11/653,830).

Canada decision, Docket T-507-05, dated Jan. 25, 2007 (Exhibit 40 to Supplemental Communication in copending U.S. Appl. No. 11/653,830).

Pfizer Canada Inc. v. *Canada (Minister of Health)*, 2006 F.C. 1471 (Exhibit 41 to Supplemental Communication in copending U.S. Appl. No. 11/653,830).

EPO Technical Opinion (Exhibit 42 to Supplemental Communication in copending U.S. Appl. No. 11/653,830).

Pfizer Complaint (Exhibit 43 to Supplemental Communication in copending U.S. Appl. No. 11/653,830).

Ranbaxy's Jan. 24, 2007 ANDA Notice Letter (from "Amendment and Response to First Reissue Office Action" in copending U.S. Appl. No. 11/653,830).

Teva's Answer (with affirmative defenses) (from "Amendment and Response to First Reissue Office Action" in copending U.S. Appl. No. 11/653,830).

English Translation of Decision in Annulment Procedure in Spain (from "Amendment and Response to First Reissue Office Action" in copending U.S. Appl. No. 11/653,830).

English Translation of Decision in Invalidation Action in South Korea (from "Amendment and Response to First Reissue Office Action" in copending U.S. Appl. No. 11/653,830).

Order Granting Request for Ex Parte Reexamination of '893 Patent (from "Amendment and Response to First Reissue Office Action" in copending U.S. Appl. No. 11/653,830).

Forest Laboratories, et al. v. Ivax Pharmaceuticals, Inc. and Cipla, Ltd., 2007 WL 2482122 (Fed. Cir. 2007) (from "Amendment and Response fo First Reissue Office Action" in copending U.S. Appl. No. 11/653,830).

Aventis Pharma Deutschland GmbH and King Pharmaceuticals, Inc. v. Lupin, Ltd. and Lupin Pharmaceuticals, Inc., 2007 WL 2593791 (Fed. Cir. 2007) (from "Amendment and Response to First Reissue Office Action" in copending U.S. Appl. No. 11/653,830).

"Exhibit 53"—Record Support for the unexpected commercial and and medical success of Lipitor® as a result of its outstanding efficacy (from "Amendment and Response to First Reissue Office Action" in copending U.S. Appl. No. 11/653,830).

"Exhibit 54"—Record Support for: (1) Lipitor®'s satisfaction of a long–felt need in the medical community to provide patients with more effective statins to help them achieve their LDL goals; and (2) unsuccessful efforts by others to satisty the long–felt need in the medical community to provide patients with more effective statins (from "Amendment and Response to First Reissue Office Action" in copending U.S. Appl. No. 11/653,830).

"Exhibit 55"—Record Support for copying (e.g., by Ranbaxy) (from "Amendment and Response to First Reissue Office Action" in copending U.S. Appl. No. 11/653,830).

"Exhibit 56"—Declaration of James Thomas Sage ((from "Amendment and Response to First Reissue Office Action" in copending U.S. Appl. No. 11/653,830).

"Exhibit 57"—Outline of Appellant's Submissions (Appeal in Australian Proceedings) (from "Amendment and Response fo First Reissue Office Action" in copending U.S. Appl. No. 11/653,830).

"Exhibit 58"—Outline of Ranbaxy's Submissions (Appeal in Australian Proceedings) (from "Amendment and Response to First Reissue Office Action" in copending U.S. Appl. No. 11/653,830).

"Exhibit 59"—Outline of Appellant's Submissions in Reply (Appeal in Australian Proceedings) (from "Amendment and Response to First Reissue Office Action" in copending U.S. Appl. No. 11/653,830).

German Decision, Oct. 29, 2007 (English Translation).

Cobalt Pharmaceuticals, Paragraph IV Certification, Oct. 24, 2007.

Takeda Chemical v. *Alpha Pharm*, 06–1329 (Fed. Cir. 2007).

Request for Reexamination of US 4,681,893.

English Language version of DK 171588 B1 (Feb. 10, 1997).

Exhibit 60—Opinion of Delaware District Court—Ranbaxy Caduet® Case (Nov. 29, 2007).

J. W. Hubbard et al.; Clinical Biochemistry, vol. 19, pp. 107–112 (Apr. 1986).

Exhibit 15C—Updates and Corrections to Previous Exhibits 15, 15A and 15B.

Complaint, Civil Action No. 07–790, United States District Court for the District of Delaware, Dec. 6, 2007 (without exhibits).

Complaint, Civil Action No. 1:07–cv–12257, United States District Court for the District of Massachusetts, Dec. 7, 2007 (without exhibits).

* cited by examiner

EX PARTE REEXAMINATION CERTIFICATE ISSUED UNDER 35 U.S.C. 307

NO AMENDMENTS HAVE BEEN MADE TO THE PATENT

AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

The patentability of claims **1–5** and **8–9** is confirmed.

Claims **6** and **7** were not reexamined.

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